EXHIBIT 1a

UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation **This Document Relates to: All Actions**	**Docket No.: 22-md-3043 (DLC)**

EXPERT REPORT OF JENNIFER A. PINTO-MARTIN, Ph.D., M.P.H.

I. PROFESSIONAL BACKGROUND AND QUALIFICATIONS

I am an epidemiologist and the Viola MacInnes/Independence Professor at the University of Pennsylvania with a joint appointment in the Nursing School and Medical School, where I teach both Epidemiology and Statistics at the graduate level. At the University of Pennsylvania, I am the Executive Director of the Center for Public Health Initiatives, which promotes interdisciplinary research, education, and practice in public health. I am also Director of the Pennsylvania Center for Autism and Developmental Disabilities, Research, and Epidemiology (PA-CADDRE). I formerly served as Chair of the Department of Biobehavioral Health Sciences in the School of Nursing and as Director of the Master of Public Health Program.

I have built a nationally and internationally recognized program of research examining two main areas: the long-term outcome of low birthweight infants and the epidemiology of neurodevelopmental disorders. I publish regularly in peer-reviewed journals in public health, pediatrics, and psychology, and have received research funding from both the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC). From 2001–2017, I served as the Principal Investigator of PA-CADDRE, one of six such centers funded by the CDC and participated in the design and data collection related to the Study to Explore Early Development (SEED). This epidemiologic study gathered genetic and risk factor data on children with autism spectrum disorder, children with other neurodevelopmental disabilities, and typically developing children.

I have extensive experience with epidemiologic studies in which exposure to various risk factors is considered in disease etiology. Many of the retrospective and prospective studies I have conducted have included data on medication exposure, and I am familiar with the methodological issues related to both the collection and analysis of these data. My regular review of epidemiologic literature also includes attention to these issues, and I have taught about the challenges related to careful collection of such data.

I serve as a peer reviewer for numerous epidemiologic journals which call upon me to evaluate the data, statistical analysis, and conclusions to determine whether they align with standard, accepted methods in epidemiology. A complete description of my professional education, training, and experiences can be found in my *curriculum vitae*.

I received an undergraduate degree from Stanford University, and a MPH and Ph.D. in Epidemiology from the School of Public Health at the University of California, Berkeley.

II. SCOPE OF REPORT AND METHODOLOGY

This report assesses whether there is credible epidemiological evidence that supports an inference of causality between maternal prenatal use of acetaminophen (also known as N-acetyl-p-aminophenol or paracetamol) and the development of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) in offspring.

To formulate my opinions, I conducted a literature review using various standard literature search tools, including EMBASE, PubMed, and PsycINFO, to identify studies that examined the association between prenatal maternal acetaminophen use and ADHD or ASD in children. I also reviewed the reference lists of individual studies, review articles, and meta-analyses to assemble a complete list of studies.

My search included the main outcomes of interest: "Autism Spectrum Disorder," "ASD," "autism," "Attention Deficit Hyperactivity Disorder," "ADHD," "Attention Deficit Disorder," and "ADD," as well as the broader category of neurodevelopmental outcome (NDD). I also searched categories of ASD described in older versions of the DSM. I combined search terms for the main outcomes of interest with the main exposure of interest: prenatal acetaminophen exposure (including N-acetyl-p-aminophenol or paracetamol). I also included search terms such as "epidemiology," "prevalence," and "etiology." I also searched risk factors for the above-mentioned outcomes of interest, including external/internal environmental factors, parental factors, birth factors, and the social environment.

After abstract review, I narrowed down the original yield to include only studies in human populations using original data on maternal prenatal acetaminophen exposure and offspring neurodevelopmental outcome. This process resulted in 14 studies on maternal prenatal acetaminophen use and offspring ADHD, 5 studies on offspring ASD, and 14 studies on offspring neurodevelopmental disorders. There was some overlap, as some studies report on more than one outcome.

My Materials Considered List, which is attached, includes all of the studies located and reviewed specifically for this matter. Additionally, I rely on my background, training, and experience as an epidemiologist specializing in autism, ADHD, and other neurodevelopmental disorders.

III. SUMMARY OF EXPERT OPINIONS

The epidemiologic evidence on prenatal exposure to acetaminophen and the risk of ASD or ADHD in offspring is not sufficient to support, and does not provide a scientifically reliable basis for, a causal inference. The reasons for this opinion include the following:

1. There are only five studies that have addressed whether in utero acetaminophen exposure increases the risk of an ASD diagnosis. Three of the five studies weigh against plaintiffs' hypothesis, and the only two studies that arguably support their positions had very weak associations and/or serious limitations that call their results into question.
2. The studies that have investigated whether acetaminophen exposure is associated with an increased risk of an ADHD diagnosis have likewise found weak and inconsistent results. Those reported findings are likely the result of residual genetic confounding, given that the only study to properly control for this possibility through use of a sibling control eliminated all statistically significant associations.
3. Studies based on data extrapolated from screening tools are not sufficient to establish a causal association between maternal acetaminophen use and the development of ASD or ADHD in children. For a diagnostic outcome such as ASD or ADHD, studies must use data based on clinical diagnoses to establish a causal link.
4. The strong genetic etiology of both ASD and ADHD is a confounder that must be accounted for in any study of child neurodevelopment, but adjusting for genetics is rarely attempted and even more rarely accomplished. One method often used to account for genetics when analyzing associations with ASD and ADHD in other contexts is the sibling control analysis. In the one study that applied a sibling control in evaluating the potential association between prenatal maternal acetaminophen use and ADHD, any noted associations disappeared.
5. Confounding by indication (where acetaminophen serves as a marker for an underlying maternal health condition) must be accounted for when analyzing the potential risk of prenatal use of acetaminophen. Because acetaminophen is used to treat the symptoms of myriad health conditions that could themselves be associated with ASD and/or ADHD, confounding by indication is present in every study I reviewed, further weighing against a causal inference.

6. Bias is also a significant concern when analyzing the weak and imprecise associations reported by the studies assessing maternal acetaminophen exposure and ASD and/or ADHD diagnosis in offspring. Misclassification bias, selection bias, and multiple comparison bias are present in nearly every study analyzing ASD and/or ADHD diagnosis.

7. Even ignoring issues of confounding and bias that most studies fail to address, the results across studies of ASD and/or ADHD are inconsistent. Some report statistically significant associations; others do not. Because the better-designed studies do not report an association, the inconsistency in the studies is an important factor that weighs against a causal conclusion.

8. There is insufficient information on exposure to perform any dose-response analysis on existing reported data. The data on exposure were collected via maternal report and through biologic sampling, both of which are unable to provide any specific information on the actual amount of acetaminophen the mothers took during pregnancy, including the number of pills taken at any given time, the strength of any pills taken, or how frequently such pills were taken. In an attempt to perform a dose-response analysis, several studies recreated dose through total days, weeks, or trimesters of use during pregnancy. These are not the types of data that can be used to analyze any purported dose-response relationship.

9. None of the remaining Bradford Hill considerations weigh in favor of a causal inference either with respect to ASD or ADHD, and several weigh against such an inference. Accordingly, a proper analysis of the available data does not support a finding of causation.

IV. EPIDEMIOLOGICAL PRINCIPLES

The discipline of epidemiology focuses on the distribution and causes of disease in a population. Unlike clinical medicine, epidemiology focuses on groups of people to look for patterns of association between risk factors and disease. Epidemiology tends to focus on diseases that have no established cure, with the goal of identifying upstream causal factors that can be modified to reduce the risk of acquiring the disease.

Epidemiologic studies begin with a hypothesis. Data are then collected among groups of people to test this hypothesis. Rates of disease are calculated in the case group and compared to the control group, and a measure of association is calculated. Statistical testing is performed to determine how confident one can be in the result. It is important to recognize that well-designed

epidemiologic studies can provide information about the association between a particular risk factor and a health outcome.

A. Epidemiologic Study Designs

Epidemiologic studies can be broadly divided into observational and experimental studies. Experimental studies attempt to control the environment through experimental manipulation, and test the association between an exposure (or a new therapy) and disease outcome. Most epidemiology, however, is observational in nature, and studies humans as they typically live their lives, assessing what they eat and drink, where they work, what medications they take, and what illnesses they develop. Observational studies include cross-sectional ecological studies, retrospective case-control studies, and prospective cohort studies. There is an inherent hierarchy in study design, with prospective cohort studies considered superior to retrospective case-control studies, which, in turn, are considered superior to cross-sectional ecological studies in terms of the quality and validity of the evidence they provide.

In observational cohort studies, participants do not have the outcome of interest to begin with and are selected based on their exposure status. They are then followed over time to evaluate for the occurrence of the outcome of interest (i.e., the disorder being studied). On the other hand, in, case-control studies, a group with a disorder (the "cases") is compared to a very similar group of individuals without the disorder (the "controls") in order to describe and analyze the difference in distribution of putative risk factors between the two groups. Thus, in a cohort study, the comparison group emerges as the study progresses and the outcome is determined, whereas in a case-control study, the comparison group is specified prior to recruitment and enrollment and is comprised of individuals without the disorder.

The question whether maternal use of acetaminophen is associated with development of ADHD or ASD in offspring has been researched through several types of observational studies. Below, I discuss the types of observational studies in reverse hierarchical order of study design (i.e., from weakest design to strongest).

1. Ecological Studies

Ecological studies are relatively quick, inexpensive, and simple to conduct, but they produce the lowest quality evidence as they are based on existing aggregate level data as opposed to individual level data. Such studies compare patterns of group-level exposures to group-level outcomes. The cross-sectional nature of ecological data, with exposure and outcome collected

simultaneously, typically does not allow for any determination of causality because it is often unclear whether the exposure preceded the outcome. Such data cannot be used to demonstrate causality between exposure and outcome because individual exposure data are not tied to individual outcomes, a requirement for demonstrating a causal link. Rather, ecological studies are used to suggest that an association *might* exist at the individual level, and can be used to develop hypotheses that can be evaluated further in studies that are more precise.

Some researchers have conducted ecological studies to explore the relationship of acetaminophen exposure to the prevalence of ASD and ADHD. One such study assessed the relationship between early neonatal acetaminophen exposure and ASD by comparing population-weighted average autism prevalence rates and male circumcision rates for all available countries and the United States as a proxy for acetaminophen exposure.[1] Another ecological study hypothesized that increases in the incidences of autism, asthma, and attention deficit disorder in the United States coincide with the replacement of aspirin by acetaminophen in the 1980s.[2] Like all ecological analyses, these data cannot demonstrate a causal relationship between maternal ingestion of acetaminophen and the development of ASD and ADHD in their offspring because they do not connect individual exposure data to individual outcomes in children. Additionally, there are many other potential reasons for the reported correlation, including, but not limited to, increased awareness of and assessment for ASD or ADHD, more systematic screening, and changes in the diagnostic criteria for ASD or ADHD, resulting in a more inclusive umbrella for affected children.[3]

2. Retrospective Case-Control Studies

In the hierarchy of study design, retrospective case-control studies are better than ecological studies. These studies begin with individuals who have the disorder (cases) and compare them to individuals without disorder (controls) with respect to exposures or risk factors

[1] Bauer AZ, Kriebel D. Prenatal and perinatal analgesic exposure and autism: an ecological link. Environ Health. 2013;12(1):41. doi:10.1186/1476-069X-12-41.

[2] Shaw W. Evidence that Increased Acetaminophen use in Genetically Vulnerable Children Appears to be a Major Cause of the Epidemics of Autism, Attention Deficit with Hyperactivity, and Asthma. J Restor Med. 2013;2(1):14-29. doi:10.14200/jrm.2013.2.0101.

[3] Maenner MJ, Shaw KA, Bakian AV, et al. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2018. MMWR Surveill Summ 2021;70(No. SS-11):1–16. DOI: http://dx.doi.org/10.15585/mmwr.ss7011a1.

of interest. The selection of the appropriate control group for a particular study is a critical step in the design of an epidemiologic study. Ideally, the control group should be as similar to the case group as possible (in terms of distribution of age, gender, ethnicity, socioeconomic status, geographic locale, etc.) except for the disorder under study. The controls need to be at risk for acquiring the disorder but must be free of the disease at the outset. For example, one might begin with a group of children who have been diagnosed with ASD and a group of typically developing children and might look back in each child's mother's prenatal records to see if the mother took hormones to help her get pregnant. The advantage of this approach is that it allows one to cast a wide net with respect to exposures of interest. After collecting data on potential risk factors, one looks to see how their distribution differs between case and controls and to test whether the relationship is statistically significant. Case-control studies can raise concerns about recall bias (cases being more likely to remember exposures than controls), although epidemiologists attempt to minimize the risks of such bias.

3. Prospective Cohort Studies

Data from prospective cohort studies are considered superior to data from ecological and case-control studies because there is less opportunity for bias, and the temporal relationship between exposure and outcome is clearly defined. As a result, this type of study is given greater credence by epidemiologists. Prospective cohort studies begin with the exposure of interest and follow those exposed forward in time to look for outcomes of interest. These studies are significantly more time-consuming and expensive, and in the case of disorders with a long latency period between exposure and manifestation of the outcome under study, they present the risk of individuals dropping out. There is a variant of this study design known as a retrospective or historical cohort study, in which a study group is enrolled on the basis of past exposure (e.g., working with known toxins in a factory) and current disease rates are assessed, eliminating the need for a long follow-up period.

4. Meta-Analyses

Meta-analyses and systematic reviews are techniques used to summarize a body of epidemiologic literature. A meta-analysis enables one to statistically combine results of comparable studies in order to increase their statistical power. However, any biases or flaws in the original studies may be amplified in such a technique and must be accounted for. Sensitivity analyses can be used to determine the magnitude of such biases, but ultimately, the results from a

meta-analysis are only as valid as its underlying data.[4] "Combining studies of poor quality with those that were more rigorously conducted may not be useful and can lead to worse estimates of the underlying truth or a false sense of precision."[5] If the data being included in a meta-analysis are flawed to begin with, the resulting summary effect will be flawed as well.

Certain researchers have conducted a series of meta-analyses an attempt to harmonize the findings from the studies addressing the impact of maternal acetaminophen use on infant neurodevelopmental outcome. However, the heterogeneity of these studies, including data related to exposure and outcome, undermines the validity of the meta-analyses. For example, combining studies with an outcome based on the results of a developmental screening test, such as the Child Behavior Checklist (CBCL), with studies using a clinical diagnosis of ASD or ADHD may introduce a level of heterogeneity that renders the results meaningless.[6]

B. Assessing Association Between Exposure And Disorder Outcome

1. Measures Of Association

After data are gathered in an epidemiologic study, a measure of association between the exposure under study and the disorder outcome of interest is calculated. This measure of association tells us the strength of the relationship and gives us an idea of how important this exposure is in the development of the disorder. The neutral value for any measure of association is 1.0; any value above 1.0 indicates that the exposure being examined correlates with an increased risk of the outcome, while any value below 1.0 indicates a potential decreased risk. It is critical to consider the statistical significance of the measure of association in order to determine whether it could have resulted by chance, as discussed in Section C.

Prospective studies derive a measure of association known as the relative risk (RR). The RR is a ratio comparing the incidence of a disorder in the exposed group to the incidence of the disorder in the unexposed group. The larger the number, the stronger the indication of risk associated with the factor. For example, a RR of 3.0 indicates that the incidence of the disorder in the exposed group is three times greater than the incidence of the disorder in the unexposed

[4] Garg AX, Hackam D, Tonelli M. Systematic review and meta-analysis: when one study is just not enough. Clin J Am Soc Nephrol. 2008 Jan;3(1):253-60. doi: 10.2215/CJN.01430307. PMID: 18178786.

[5] Elsayir, Habib. (2015). Significance Test in Meta-analysis Approach: A theoretical Review. Statistics: A Journal of Theoretical and Applied Statistics. 4. 630-639. 10.11648/j.ajtas.20150406.35.

[6] Lee YH. Strengths and limitations of meta-analysis. Korean J Med 2019;94(5):391-395.

group; in other words, there is a three-fold elevation of risk for the disease associated with the exposure. A RR is a measure of association that can only be derived from a prospective study because it relies on the calculation of the incidence of a disorder, that is, the number of new cases of disease arising in the population over time. Epidemiologists also have a method to estimate the relative risk from retrospective studies, referred to as the odds ratio (OR). The OR represents the odds that the disorder will occur given the exposure, compared to the odds of the disorder occurring without the exposure. A similar measure is the hazard ratio (HR). The HR allows for a measure of the temporal progression of an outcome within a group. It compares events per time period in two groups, and thus captures the evolution of events as opposed to what is present at the end of the follow-up period.

Epidemiologists commonly use two-by-two tables to measure an association (RR or OR). Below is an example for illustration.

	Disorder (D)	**No Disorder (ND)**
Exposure (E)	A n=20	B n=10
No exposure (NE)	C n=130	D n=140
TOTAL	150	150

In this table, the columns represent disorder (D) and no disorder (ND), and the rows represent exposure (E) and no exposure (NE). Study subjects are enrolled based upon disorder status. In this example, the researchers enrolled 150 cases with the disorder and 150 controls without the disorder and assessed exposure to a risk factor. To calculate the measure of association between the risk factor and the disorder, we create a ratio comparing the evidence in favor of the association with the evidence against the association. This table shows that cells "A" and "D" hold evidence in favor of the hypothesized association, i.e., they represent cases with the disorder who were exposed to the risk factor and controls without disorder who were not exposed. On the other hand, cells "B" and "C" contain evidence that runs counter to the hypothesized association; they contain patients with disorder who were not exposed to the risk factor and patients without disorder who were exposed.

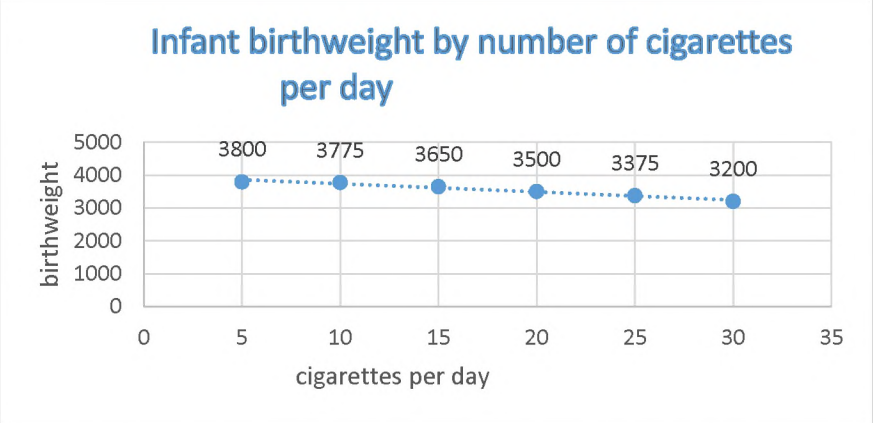
The OR is calculated by using the formula: A x D / B x C. In other words, we put the evidence in favor of the association in the numerator of the equation and put the evidence against

the association in the denominator of the equation. If the two values are essentially equal, meaning that the evidence in support of an association between exposure and outcome equals the evidence against the hypothesized association, the OR will be 1.0. If the evidence in favor of an association is stronger than the evidence against the association, then the OR will exceed 1.0. In this hypothetical illustration, the OR equals 2.15, indicating there is more than a doubling of a risk of disease among those exposed to the risk factor.

2. Beta Coefficient

Another way to measure the association between the exposure under study and the disorder of interest is a beta (β) coefficient. In studies with a continuous outcome, such as IQ or birthweight, a statistical technique known as linear regression analysis will yield a beta coefficient, a measure of the change in the outcome (y) for every unit change in the predictor (x). The standardized beta coefficient reveals the amount the outcome variable changes in response to a one standard deviation change in x. The standardized beta coefficient will range from 0 to 1 or 0 to -1, depending on the direction of the relationship. The closer the value is to 1 or -1, the stronger the relationship.

For example, we might want to assess the association between offspring birthweight in grams (y) and maternal prenatal smoking, measured as number of cigarettes per day (x). A scatterplot is a graphic representation of this relationship, as shown below. The more spread out the data are, the less likely that a statistically significant association between the exposure and the disorder of interest will be found. In this hypothetical example we can see a strong dose-response relationship.



The linear regression model determines whether the variables maternal prenatal smoking (x) and offspring birthweight (y) are systematically and significantly related. The beta

coefficient provides an estimate of the effect of x on y. The standard error for beta is a measure of the spread of the points from the regression line. In this hypothetical example, beta= - 20, which tells us that for every additional cigarette smoked by the mother, the birthweight of the infant is reduced by 20 grams, with a standard error of ±05.

The impact of confounders can be addressed through a multiple linear regression model, an extension of a simple model, where instead of only one explanatory variable (e.g., maternal prenatal smoking) several explanatory variables (e.g., maternal prenatal smoking, alcohol and drug use, and maternal age at birth) are considered simultaneously.

C. Calculating Statistical Significance

Statistical significance is a measure for evaluating the likelihood of whether an association has been arrived at by chance, or instead is evidence supporting an increase (or decrease) in the risk of disorder associated with the exposure. Epidemiologists typically use the 95% confidence interval to answer this question. This interval represents the possible range of values that the RR or might take on if the study were repeated 100 times. If the interval is tight around the derived RR or, then we have confidence that our result is precise and is unlikely to be a chance finding. If the interval of a statistically significant association is large, it indicates that this measure is unstable and may not reflect the true association between exposure and disease. If the interval includes 1.0, we cannot exclude the null hypothesis of no association between the exposure and the outcome, as the value obtained from the study is likely due to chance. This is known as lack of statistical significance.

Statistical significance is also sometimes represented by the "p-value." This is a number calculated from a statistical test that describes how likely it is that the result obtained from the data would occur if the null hypothesis of no association were true. For example, using the exemplar study discussed above, if the null hypothesis states that there is no relationship between exposure and disorder, the alternative hypothesis, sometimes known as the research hypothesis, would state that the exposure to the risk factor is associated with an increase in the risk of the disorder. Epidemiologists typically accept a p-value of less than 5% as evidence that the null hypothesis can be rejected in favor of the research hypothesis. By doing so, we are acknowledging the fact that there is less than 5% chance that we could make an error in accepting the research hypothesis when it is not true, something known as a Type I error (i.e., false positive). The smaller the p-value, the more likely epidemiologists will reject the null hypothesis, whereas a p-value greater than 5% is

not considered statistically significant and we are typically unwilling to reject the null hypothesis of no association. In the example above, the 95% confidence interval is calculated to equal 0.98 to 4.9 and the p-value is calculated to be greater than 0.05, telling us that the result of OR= 2.15 is likely due to chance and likely does not represent any real evidence of an increased risk of a disorder associated with the exposure of interest.

In situations where multiple hypotheses are tested on the same set of data, there is an increased likelihood of obtaining a statistically significant result by chance alone (specifically, one out of twenty tests would be expected to be statistically significant by chance). In these circumstances, a correction known as the Bonferroni (or multiplicity) adjustment should be employed. This adjustment divides the p-value by the number of tests performed to account for the increased likelihood of a chance finding. In the case of ORs, the method narrows the acceptable interval to a stricter 97.5%.[7]

I note that plaintiff's expert, Andrea Baccarelli, asserts that the "modern approach is not to treat p-values—and in particular, a p-value of 0.05—as a touchstone for whether a result is valid."[8] He cites nothing in support of this statement. While it is true that scientists have debated the strengths and weaknesses of measures of statistical significance in recent years, it remains standard practice to differentiate between results based on whether they meet generally-accepted measures of significance, including a p-value of 0.05 specifically. In a recent clarification of its statistical reporting guidelines, for example, the *New England Journal of Medicine*—arguably one of the leading medical journals—clarified that, despite acknowledged limitations, "P values continue to have an important role in medical research, and we do not believe that P values and significance tests should be eliminated altogether."[9] If anything, the problem with the 0.05 p-value identified by the *Journal* is its propensity to produce *false positives* because it is not sufficiently exacting—specifically when adjustments for multiplicity are not made.[10] As I discuss later in this report, this problem (i.e., a failure to adjust for multiplicity) runs rampant throughout the ASD and ADHD

[7] Armstrong RA. When to use the Bonferroni correction. Ophthalmic Physiol Opt. 2014 Sep;34(5):502-8.

[8] Expert Report of Andrea Baccarelli, MD, PhD, MPH at 58.

[9] Harrington D, D'Agostino RB Sr, Gatsonis C, Hogan JW, Hunter DJ, Normand ST, Drazen JM, Hamel MB. New Guidelines for Statistical Reporting in the Journal. N Engl J Med. 2019 Jul 18;381(3):285-286. doi: 10.1056/NEJMe1906559. PMID: 31314974.

[10] Harrington D, D'Agostino RB Sr, Gatsonis C, Hogan JW, Hunter DJ, Normand ST, Drazen JM, Hamel MB. New Guidelines for Statistical Reporting in the Journal. N Engl J Med. 2019 Jul 18;381(3):285-286. doi: 10.1056/NEJMe1906559. PMID: 31314974.

literature examining acetaminophen use. Thus, to the extent Dr. Baccarelli's suggestion about p-values has merit, the concern would be that any associations in the literature are far more likely to be erroneously reported as statistically significant.

There is another type of statistical error known as a Type II error in which a conclusion to accept the null hypothesis of no association is reached when, in fact, an association does exist (i.e., false negative). This is a function of the statistical power of the study, which is related to the study's sample size and other factors.

D. Bias

Bias is defined as any systematic error in an epidemiological study that results in an incorrect estimate of the association between exposure and risk of the disorder. Bias can pose a greater threat to the validity of reported findings than the random variability reflected by p-values and confidence intervals.[11] Because there are few methods to adjust for bias after the data have been collected, careful consideration of the ways in which bias may be introduced during the design and conduct of the study is essential to limit the impact on the validity of the study results.

1. Misclassification Bias

Misclassification bias occurs in relation to both the exposure and the outcome under study and can be either differential or non-differential. Non-differential exposure misclassification occurs if there is roughly equal misclassification between subjects that have or do not have the health outcome under study (e.g., women who do or do not have a child with a diagnosis of ASD or ADHD). When the error in reporting of exposure is random and equally distributed between the two groups, misclassification will usually (but not always) bias the results towards the null. Conversely, if the error in reporting is not equally distributed (e.g., mothers with anxiety are more likely to use, and recall using, acetaminophen during pregnancy and are more likely to have a child with ASD or ADHD), differential misclassification occurs. Differential misclassification can bias the measure of association (RR or OR) either towards or away from the null, depending on the proportions of subjects misclassified.

[11] Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, Altman DG. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol. 2016 Apr;31(4):337-50. doi: 10.1007/s10654-016-0149-3. Epub 2016 May 21. PMID: 27209009; PMCID: PMC4877414.

2. Information Bias

Information bias occurs when there are systematic differences in the way information is collected for the groups being studied. This bias can arise when collecting data on exposure or outcome. For example, it has been shown that mothers of children who are born at low birthweight are more likely to identify abnormal behaviors in screening instruments or questionnaires, likely due to their heightened anxiety about the child's developmental trajectory. One method to attempt to control for the potential for a biased outcome assessment is to have more than one informant. This is often a combination of parents, health care providers, or teachers. When the reported behavioral profiles differ, it can be a signal of biased assessment. For example, in Parker et al. 2020, associations that were present using data from maternal report did not exist when data from teacher report was analyzed.[12]

3. Recall Bias

Recall bias is a particular form of information bias that leads to either an underestimate or overestimate of the association between exposure and outcome. In a case-control study or cohort study, because data on exposure are collected retrospectively, the quality of the data is often determined by an individual's ability to accurately recall past exposure(s). Recall bias occurs when the information provided on exposure is different between the cases and controls. If the cases tend to have a better recall on past exposures than controls, it will lead to an overestimation of the association between exposure and outcome. For example, it has been shown repeatedly that women who suffer an adverse pregnancy outcome will scrutinize the past to try to recall what might have caused the problem. As stated, the psychological profile of the mother herself may also affect recall, as there is evidence that women with underlying anxiety are more prone to recall adverse events during their pregnancy.[13] These examples can lead to differential recall of past exposures between cases (women with the adverse outcome or different psychological profiles) and controls. Therefore, to claim recall bias is non-differential in the studies assessing maternal

---

[12] Parker SE, Collett BR, Werler MM. Maternal acetaminophen use during pregnancy and childhood behavioural problems: Discrepancies between mother- and teacher-reported outcomes. Paediatr Perinat Epidemiol. 2020;34(3):299-308. doi:10.1111/ppe.12601.

[13] de Graaf R, Bijl RV, Smit F, Ravelli A, Vollebergh WA. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Am J Epidemiol. 2000 Dec 1;152(11):1039-47. doi: 10.1093/aje/152.11.1039. PMID: 11117613.

Dupuis M, Strippoli MP, Gholam-Rezaee M et al. Mental disorders, attrition at follow-up, and questionnaire non-completion in epidemiologic research Int J Methods Psychiatr Res. 2019;28:e1805.

acetaminophen use and development of ASD or ADHD in offspring would be purely speculative, improper, and contrary to the available data that address that question.

4. Selection Bias

Selection bias occurs when there are differences in the characteristics between those who are selected and/or participate in a study and those who are not selected and/or do not participate, and those characteristics are related to either the exposure or outcome under investigation.

One form of selection bias is loss to follow-up in longitudinal studies. This refers to those individuals who drop out of a study and for whom no further data can be gathered. This is a particular problem associated with cohort studies because follow-up to determine the outcome under investigation is essential. Bias can be introduced if the individuals lost to follow-up differ with respect to the exposure and/or outcome from those who remain in the study. For example, research on retention and attrition in longitudinal studies has shown that individuals with anxiety are less likely to drop out. If the individuals that are retained by the study have higher rates of anxiety or depression, which is also associated with offspring neurobehavioral disorders, the bias will be differential.[14]

E. Confounding

Confounding refers to the possibility that an observed association is due, either in full or in part, to the effect of another variable that differs between the study groups. Sometimes referred to as a "lurking variable," it affects both the likelihood of exposure and the risk of developing the outcome. That variable might be another exogenous exposure or, more commonly, a characteristic of the individuals in the study (e.g., gender, age, socioeconomic status, co-morbid medical conditions including depression or anxiety). Examples of both exogenous and endogenous confounders are illustrated below.

The end-result is that the estimated association is not the same as the true effect.

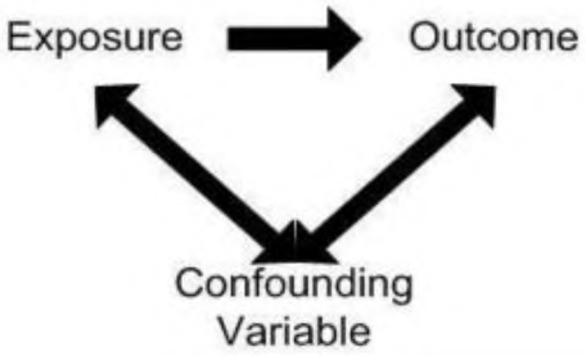
---

[14] de Graaf R, Bijl RV, Smit F, Ravelli A, Vollebergh WA. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Am J Epidemiol. 2000 Dec 1;152(11):1039-47. doi: 10.1093/aje/152.11.1039. PMID: 11117613.

Dupuis M, Strippoli MP, Gholam-Rezaee M et al. Mental disorders, attrition at follow-up, and questionnaire non-completion in epidemiologic research Int J Methods Psychiatr Res. 2019;28:e1805;

Bekkhus M, Lee Y, Nordhagen R, Magnus P, Samuelsen SO, Borge AIH. Re-examining the link between prenatal maternal anxiety and child emotional difficulties, using a sibling design. Int J Epidemiol. 2018 Feb 1;47(1):156-165. doi: 10.1093/ije/dyx186. PMID: 29024982; PMCID: PMC5837524.

Confounding can lead us to believe that there is a valid statistical association when one does not exist, or alternatively that there is no association when one is truly present. This diagram[15] demonstrates confounding.



For a variable to be considered as a confounder, the variable:

- Must be independently associated with the outcome (be a risk factor).
- Must be associated with the exposure under study in the source population.
- Must not lie on the causal pathway between exposure and disease.[16]

To the extent possible, confounding factors related to ASD or ADHD should be accounted for collectively. As one very recent study finding an association between the mother's neuroticism and her more frequent use of acetaminophen emphasized, "the role of other unmeasured confounders such as familial environment and genetics has been shown to be substantial (Leppert et al. 2019)" in ADHD, and, "[t]aken together, these findings underscore the need of triangulating the evidence using different causally informative approaches and in light of possible biases introduced by numerous unmeasured confounders."[17]

1. Confounding By Indication

Confounding by indication is a particular type of confounding whereby the exposure being assessed is linked to an underlying health condition (i.e., indication for use) that, in itself, is a risk

[15] Barratt, H. Kirwan, M. Bias and Confounding. *Biases and Confounding | Health Knowledge*, https://www.healthknowledge.org.uk/public-health-textbook/research-methods/1a-epidemiology/biases

[16] Barratt, H. Kirwan, M. Bias and Confounding. *Biases and Confounding | Health Knowledge*, https://www.healthknowledge.org.uk/public-health-textbook/research-methods/1a-epidemiology/biases

[17] Lupattelli A, Trinh NTH, Nordeng H. Association of maternal personality traits with medication use during pregnancy to appraise unmeasured confounding in long-term pharmacoepidemiological safety studies. Front Pharmacol. 2023 May 15;14:1160168. doi: 10.3389/fphar.2023.1160168. PMID: 37256227; PMCID: PMC10225644.

factor for the outcome. An example from my own research that can illustrate this concept is the supposed impact of SSRI use during pregnancy on the risk of ASD.[18]

Depression and its treatment with antidepressants have increased over the past two decades. SSRIs are commonly used to manage depression during pregnancy. Initially, evidence from several population-based studies indicated that prenatal exposure to SSRI increased the risk of ASD in offspring.[19] However, there was still debate as to whether the treatment itself, or the underlying indication for treatment—i.e., the psychiatric disorder—was the etiologically relevant factor.

To investigate this issue, my research group analyzed data from the Study to Explore Early Development, a multi-site case-control study conducted in six sites across the United States among children born between 2003-2011. Children were enrolled at 2-5 years of age. Final study group classification (ASD or control) was determined by an in-person standardized developmental assessment by a medical provider. Maternal history of psychiatric disorders and use of

---

[18] Ames J, Ladd-Acosta C, Fallin MD, Qian Y, Schieve LA, DiGuiseppi C, PhD4, Li- LeeC, Kasten E, Zhou G, Pinto-Martin J, Howerton E, Eaton C, Croen L.Maternal Psychiatric Conditions, Treatment with SSRIs, and Neurodevelopmental Disorders Biol Psychiatry. 2021 August 15; 90(4): 253–262.

[19] Sørensen MJ, Grønborg TK, Christensen J, Parner ET, Vestergaard M, Schendel D, Pedersen LH (2013): Antidepressant exposure in pregnancy and risk of autism spectrum disorders. Clin Epidemiol 5:449–459.

Hviid A, Melbye M, Pasternak B (2013): Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism. N Engl J Med. 369:2406–2415.

Malm H, Brown AS, Gissler M, Gyllenberg D, Hinkka-Yli-Salomäki S, McKeague IW, et al. (2016): Gestational exposure to selective serotonin reuptake inhibitors and offspring psychiatric disorders: A national register-based study. J Am Acad Child Adolesc Psychiatry 55:359– 366.

Viktorin A, Uher R, Reichenberg A, Levine SZ, Sandin S (2017): Autism risk following antidepressant medication during pregnancy. Psychol Med 47:2787–2796.

Brown HK, Ray JG, Wilton AS, Lunsky Y, Gomes T, Vigod SN (2017): Association between serotonergic antidepressant use during pregnancy and autism spectrum disorder in children. JAMA 317:1544– 1552.

Sujan AC, Rickert ME, Öberg AS, Quinn PD, Hernández-Díaz S, Almqvist C, Lichtenstein P, Larsson H, D'Onofrio BM. Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring. JAMA. 2017 Apr 18;317(15):1553-1562. doi: 10.1001/jama.2017.3413. PMID: 28418479; PMCID: PMC5875187.

Sullivan F, Magnusson C, Reichenberg A et al. Family History of Schizophrenia and Bipolar Disorder as Risk Factors for Autism. Arch Gen Psychiatry. 2012;69(11):1099-1103

Hagberg KW, Robijn AL, Jick S (2018): Maternal depression and antidepressant use during pregnancy and the risk of autism spectrum disorder in offspring. Clin Epidemiol. 10:1599–1612.

Morales DR, Slattery J, Evans S, Kurz X (2018): Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: systematic review of observational studies and methodological considerations. BMC Med. 16:6.

antidepressants during pregnancy were ascertained in three ways: maternal telephone interview shortly after study enrollment, self-report on maternal medical history form, and review of maternal medical records. During the interview, the mother was also asked to specify the type of psychiatric illness and date of onset, and types and timing of antidepressant medications taken during pregnancy. Covariates in adjusted analyses included maternal race, education, age at delivery, history of smoking, and household income during pregnancy.

	ASD CASE (n=1367)	**CONTROL (n=1671)**	**OR (95% CI)**
Maternal psychiatric condition (with or without SSRI use)	348	264	1.93 (1.59-2.34)
Maternal psychiatric condition with no SSRI use	223	177	1.81 (1.44–2.27)
SSRI use in only those with maternal psychiatric condition	115	81	1.14 (0.80-1.62)

The results indicated that the adjusted odds of having a child with ASD were nearly two-fold higher among mothers with a history of psychiatric illness prior to the delivery of the study child, irrespective of SSRI use (OR = 1.93, 95% CI 1.59, 2.34). Higher odds were also observed among mothers with psychiatric illness who did not use SSRIs during pregnancy (OR = 1.81, 95% CI 1.44, 2.27). However, when the analysis was restricted to mothers with a psychiatric condition, the odds of ASD were not higher among children prenatally exposed to SSRIs (OR = 1.14, 95% CI 0.8, 1.62). In other words, there was no evidence that prenatal exposure to SSRIs is associated with increased risk of ASD independent of the indication for treatment.[20] Other studies have reached similar conclusions.[21]

[20] Ames J, Ladd-Acosta C, Fallin MD, Qian Y, Schieve LA, DiGuiseppi C, PhD4, Li- LeeC, Kasten E, Zhou G, Pinto-Martin J, Howerton E, Eaton C, Croen L.Maternal Psychiatric Conditions, Treatment with SSRIs, and Neurodevelopmental Disorders Biol Psychiatry. 2021 August 15; 90(4): 253–262.

[21] Hviid A, Melbye M, Pasternak B (2013): Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism. N Engl J Med. 369:2406–2415.

Sørensen MJ, Grønborg TK, Christensen J, Parner ET, Vestergaard M, Schendel D, Pedersen LH. Antidepressant exposure in pregnancy and risk of autism spectrum disorders. Clin Epidemiol. 2013 Nov 15;5:449-59. doi: 10.2147/CLEP.S53009. PMID: 24255601; PMCID: PMC3832387.

Confounding by indication must be accounted for when assessing the impact of prenatal acetaminophen use on the potential risk of offspring ASD or ADHD. The possibility of confounding by indication, whereby acetaminophen is a marker for the underlying health condition, but is not causally related to the outcome, is significant and difficult to address in the absence of reliable data on the underlying infections/illness. Because the studies assessing the risk of prenatal acetaminophen exposure rely almost exclusively on maternal recall of illness and infection during pregnancy, there is a substantial likelihood of bias. To adequately assess the impact of such bias would require a carefully designed prospective study of pregnant women with ongoing data collection on any illness and medication use throughout gestation. Instead, we currently have only data based on retrospective recall of both illness and acetaminophen use. It is quite likely that such recall is influenced by a multitude of factors, including timing, length and severity of the illness, the length of time since the incident and the recall of the information, and importantly, the psychological profile of the mother herself. The timing of infections can also have a strong influence on the prenatal effects as fetal brain development may have specific windows of vulnerability.

The importance of controlling for confounding by indication in assessing the relationship between prenatal acetaminophen use and offspring neurodevelopmental outcome was demonstrated in an analysis by Zerbo et al. 2013 using data from the CHARGE Study in California. The authors assessed the risk of ASD and developmental delay (DD) associated with influenza and fever. Though neither ASD nor DD was associated with influenza alone, both were associated

---

Clements CC, Castro VM, Blumenthal SR, Rosenfield HR, Murphy SN, Fava M, et al. (2015): Prenatal antidepressant exposure is associated with risk for attention-deficit hyperactivity disorder but not autism spectrum disorder in a large health system. Mol Psychiatry 20:727– 734.

Malm H, Brown AS, Gissler M, Gyllenberg D, Hinkka-Yli-Salomäki S, McKeague IW, et al. (2016): Gestational exposure to selective serotonin reuptake inhibitors and offspring psychiatric disorders: A national register-based study. J Am Acad Child Adolesc Psychiatry 55:359– 366.

Viktorin A, Uher R, Reichenberg A, Levine SZ, Sandin S. Autism risk following antidepressant medication during pregnancy. Psychol Med. 2017 Dec;47(16):2787-2796. doi: 10.1017/S0033291717001301. Epub 2017 May 22. PMID: 28528584; PMCID: PMC6421839.

Brown HK, Ray JG, Wilton AS, Lunsky Y, Gomes T, Vigod SN (2017): Association between serotonergic antidepressant use during pregnancy and autism spectrum disorder in children. JAMA 317:1544– 1552.

Sujan AC, Rickert ME, Öberg AS, Quinn PD, Hernández-Díaz S, Almqvist C, Lichtenstein P, Larsson H, D'Onofrio BM. Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring. JAMA. 2017 Apr 18;317(15):1553-1562. doi: 10.1001/jama.2017.3413. PMID: 28418479; PMCID: PMC5875187.

with maternal fever during pregnancy: ASD (OR = 2.12, 95% CI 1.17, 3.84); DD (OR = 2.50, 95% CI 1.20, 5.20). The fever-associated ASD risk was attenuated among mothers who reported taking fever-reducing medications (OR = 0.30, 95% CI 0.59, 2.84), but remained elevated for those who did not (OR = 2.55, 95% CI 1.30, 4.99). In addition, a recent meta-analysis of the association between fever during pregnancy and risk of ASD in offspring concluded that a modest but statistically significant risk exists, and that the risk does not vary by type of infection or by timing during pregnancy. The authors also report that the combined effect of maternal fever during pregnancy was somewhat stronger than the effect for "any infection," perhaps indicating that fever is more proximal to autism in the causal pathway and therefore could be an important mediator of infection.[22]

2. Residual Confounding

Residual confounding occurs when a confounder has not been adequately adjusted for in the analysis, leading to a distortion of the results. The extent to which a variable retains this ability of residual confounding is due, in part, to how adequately it has been measured in the data gathering phase.

To guard against residual confounding, it is essential that known risk factors for ASD and ADHD be accounted for in any epidemiologic study. If data on a particular covariate or confounder are not collected, we have no ability to test for its impact on the measure of association we calculate.

V. METHODS TO ADDRESS CONFOUNDING CHALLENGES

None of the cohorts from which data were analyzed in the cohort studies examining the risk of prenatal maternal acetaminophen use and childhood ASD and ADHD were specifically designed to assess this exposure and outcome. Therefore, most failed to account for known and significant confounders, such as genetics. This is a noteworthy concern because maternal behavior and lifestyle during pregnancy may be related to the same genetic factors that pre-dispose offspring to developing ASD and ADHD.[23] There are several different study designs and statistical

[22]Tioleco N, Silberman AE, Stratigos K, Banerjee-Basu S, Spann MN, Whitaker AH, Turner JB. Prenatal maternal infection and risk for autism in offspring: A meta-analysis. Autism Res. 2021 Jun;14(6):1296-1316. doi: 10.1002/aur.2499. Epub 2021 Mar 15. PMID: 33720503.

[23] Leppert B, Havdahl A, Riglin L, et al. Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures. JAMA Psychiatry. 2019;76(8):834. doi:10.1001/jamapsychiatry.2019.0774.

techniques available to address the problem of residual or unmeasured confounding in epidemiological studies, including sibling control analysis, negative control, and sensitivity analysis.

A. Sibling Control For Residual Confounding

A sibling control analysis is often used in epidemiologic research as a technique for addressing unmeasured confounders, such as genetics. The sibling control method does this by analyzing siblings that are discordant for both the exposure and outcome being studied. For example, Von Ehrenstein et al. used a sibling control design to assess smoking as a risk factor for ASD, comparing the outcome between siblings born of the same mother, where the mother smoked in some but not all pregnancies. This allowed the author to determine whether smoking had an independent effect on the risk of offspring ASD.[24] Because the mother remains the same in such analyses, any association found between prenatal smoking and risk of development of ASD in the sibling comparison would not be influenced by factors that are constant between pregnancies, including maternal genetics, neuropsychiatric traits, and socioeconomic status.

A number of potential risk factors for ASD and ADHD have been identified in published epidemiological studies. More recently, sibling control studies showed that these associations were confounded and not representative of an independent risk. *See* Zhang et al. 2021 (ASD and c-section);[25] Skoglund et al. 2014 (ADHD and smoking);[26] Wiggs et al. 2017 (ASD and labor induction);[27] Gardner et al. 2015 (ASD and Maternal BMI).[28]

---

[24] von Ehrenstein OS, Cui X, Yan Q, et al. Maternal prenatal smoking and autism spectrum disorder in offspring: a California statewide cohort and sibling study. Am J Epidemiol. 2021;190:728–737.

[25] Zhang T, Brander G, Mantel Ä, Kuja-Halkola R, Stephansson O, Chang Z, Larsson H, Mataix-Cols D, Fernández de la Cruz L. Assessment of Cesarean Delivery and Neurodevelopmental and Psychiatric Disorders in the Children of a Population-Based Swedish Birth Cohort. JAMA Netw Open. 2021 Mar 1;4(3):e210837. doi: 10.1001/jamanetworkopen.2021.0837. PMID: 33666663; PMCID: PMC7936261.

[26] Skoglund C, Chen Q, D'Onofrio BM, Lichtenstein P, Larsson H. Familial confounding of the association between maternal smoking during pregnancy and ADHD in offspring. J Child Psychol Psychiatry. 2014;55(1):61–8.

[27] Wiggs KK, Rickert ME, Hernandez-Diaz S, Bateman BT, Almqvist C, Larsson H, Lichtenstein P, Oberg AS, D'Onofrio BM. A Family-Based Study of the Association Between Labor Induction and Offspring Attention-Deficit Hyperactivity Disorder and Low Academic Achievement. Behav Genet. 2017 Jul;47(4):383-393. doi: 10.1007/s10519-017-9852-4. Epub 2017 May 27. PMID: 28551761 (ASD and labor induction).

[28] Gardner RM, Lee BK, Magnusson C, Rai D, Frisell T, Karlsson H, Idring S, Dalman C. Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: Results from a Swedish total population and discordant sibling study. Int J Epidemiol. 2015 Jun;44(3):870-83. doi: 10.1093/ije/dyv081. Epub 2015 Jun 4. PMID: 26045508; PMCID: PMC4521130.

There is no debate that genetics plays a significant role in the etiology of ASD and ADHD. Despite this fact, few studies have sufficiently attempted to address residual confounding due to familial/genetic factors. Notably, several studies demonstrated clear evidence of residual confounding through the use of sibling controls, polygenic risk scores, and negative exposure controls.[29] In these studies, the reported association was substantially attenuated after the appropriate adjustment was performed. These results reveal that studies that report an association between prenatal acetaminophen exposure and an increased risk of development of ASD or ADHD in offspring without sufficiently accounting for familial/genetic factors are likely to be compromised by residual confounding and therefore are of limited value as evidence of causality.

B. Negative Control For Residual Confounding

Negative Control Exposure (NCE) is another technique used to address unmeasured confounding. NCE studies evaluate exposures that are not expected to be associated with the outcome. For example, epidemiologic studies of intrauterine exposure on offspring outcomes compare the association of a maternal exposure during pregnancy to that of paternal exposure with the outcome of interest. If an association is found between paternal exposure and the outcome of interest (particularly if the magnitude of the association is similar to that with maternal exposure), this suggests that unmeasured confounding is influencing the results. One requirement with the NCE approach is that the potential confounder should be time-invariant. In other words, the potential confounder should not change from pre-pregnancy to pregnancy to post-pregnancy.

A paternal negative control exposure can be used to help test whether residual or unmeasured confounding accounts for the association seen between maternal acetaminophen exposure and offspring neurodevelopment. Although it has been hypothesized that paternal exposure to acetaminophen may alter the sperm, there is no evidence to support that a father's exposure to acetaminophen during the mother's pregnancy would increase the risk of the child's development of ADHD or ASD. Therefore, any association seen between the father's use of acetaminophen and ADHD or ASD development in childhood suggests residual confounding. Two studies relied on by plaintiffs' experts, Stergiakouli 2016 and Ystrom 2017, reported

[29] Leppert et al. 2019; Trønnes JN, Wood M, Lupattelli A, Ystrom E, Nordeng H. Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children. Paediatr Perinat Epidemiol. 2020;34(3):247-256. doi:10.1111/ppe.12568.

Gustavson K, Ystrom E, Ask H, et al. Acetaminophen use during pregnancy and offspring attention deficit hyperactivity disorder – a longitudinal sibling control study. JCPP Adv. 2021;1(2). doi:10.1002/jcv2.12020.

associations between fathers' acetaminophen use and development of ADHD or ASD in offspring.[30]

In some of the studies investigating the potential association between maternal acetaminophen use and ASD and/or ADHD development in children, maternal exposure prior to pregnancy or after delivery has been used as a putative negative control on the theory that use of the acetaminophen during these time periods could not be associated with the child's outcome.[31] But there are important differences between pregnant women and non-pregnant women that can affect acetaminophen use, undermining this negative control design. It is well-understood that pregnancy brings a host of physiologic, psychologic, and lifestyle changes that alter a pregnant woman's body, environment, and response to her environment. These changes cause an increase in the proportion of women who suffer from pain, anxiety, and depression.[32] Further, while chronic illness may continue into and beyond pregnancy, the medications used to treat these illnesses do not remain constant (e.g., the standard treatment of rheumatoid arthritis, such as steroids or NSAIDs, cannot continue throughout pregnancy). This difference is supported by multiple studies. In the Norwegian Birth Cohort, approximately 46% of women used

---

[30] Stergiakouli E, Thapar A, Davey Smith G. Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding. JAMA Pediatr. 2016;170(10):964. doi:10.1001/jamapediatrics.2016.177.

Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, Davey Smith G, Stoltenberg C, Surén P, Håberg SE, Hornig M, Lipkin WI, Nordeng H, Reichborn-Kjennerud T. Prenatal Exposure to Acetaminophen and Risk of ADHD. Pediatrics. 2017 Nov;140(5):e20163840. doi: 10.1542/peds.2016-3840. PMID: 29084830; PMCID: PMC5654387.

[31] Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, Davey Smith G, Stoltenberg C, Surén P, Håberg SE, Hornig M, Lipkin WI, Nordeng H, Reichborn-Kjennerud T. Prenatal Exposure to Acetaminophen and Risk of ADHD. Pediatrics. 2017 Nov;140(5):e20163840. doi: 10.1542/peds.2016-3840. PMID: 29084830; PMCID: PMC5654387.

Chen MH, Pan TL, Wang PW, et al. Prenatal Exposure to Acetaminophen and the Risk of Attention-Deficit/Hyperactivity Disorder: A Nationwide Study in Taiwan. *J Clin Psychiatry*. Published online 2019:7.

Liew Z, Kioumourtzoglou MA, Roberts AL, O'Reilly ÉJ, Ascherio A, Weisskopf MG. Use of Negative Control Exposure Analysis to Evaluate Confounding: An Example of Acetaminophen Exposure and Attention-Deficit/Hyperactivity Disorder in Nurses' Health Study II. Am J Epidemiol. 2019;188(4):768-775. doi:10.1093/aje/kwy288.

Trønnes JN, Wood M, Lupattelli A, Ystrom E, Nordeng H. Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children. Paediatr Perinat Epidemiol. 2020 May;34(3):247-256. doi: 10.1111/ppe.12568. Epub 2019 Aug 25. PMID: 31448449; PMCID: PMC8285062.

[32] Treatment and management of mental health conditions during pregnancy and postpartum. Clinical Practice Guideline No. 5. American College of Obstetricians and Gynecologists. Obstet Gynecol 2023; 141: 1262– 88. doi: 10.1097/AOG.0000000000005202.

acetaminophen during pregnancy, but only 26% of women used acetaminophen six months before pregnancy.[33] In the Copenhagen Pregnancy Cohort, approximately 33% of women who used acetaminophen three months prior to pregnancy had chronic medical diseases, but 57% of women who used acetaminophen during the first trimester had chronic medical diseases. Additionally, women with chronic medical disorders were more likely to use acetaminophen (migraine aOR = 4.39, CI 95% 3.20, 6.02; rheumatoid arthritis aOR = 4.32, 95% CI 2.41, 7.72; and mental diseases aOR = 2.74, CI 95% 1.67, 4.49).[34] Pregnancy can induce or exacerbate stress, which could, in turn, have an impact on acetaminophen consumption.

Data from Stergiakouli et al. 2016 clearly establish that women who use acetaminophen during pregnancy are different from those who use acetaminophen after pregnancy:

Characteristic	Percentage of Women with Characteristic Who Used Acetaminophen	
	At 32 Weeks of Pregnancy	**Postnatal Use**
Socioeconomic Status (Low)	16.3%	42%
Socioeconomic Status (High)	41.1%	15.5%
Psychiatric Illness	10.2%	8.1%
Smoking	21.3%	18.6%
Alcohol Consumption	59.9%	56.4%

For all of these reasons, the potential confounding factors cannot be said to be time-invariant; to the contrary, they may change between pregnancy and non-pregnancy. Put another way: women who use acetaminophen before pregnancy are not similarly situated to those who

[33] Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, Davey Smith G, Stoltenberg C, Surén P, Håberg SE, Hornig M, Lipkin WI, Nordeng H, Reichborn-Kjennerud T. Prenatal Exposure to Acetaminophen and Risk of ADHD. Pediatrics. 2017 Nov;140(5):e20163840. doi: 10.1542/peds.2016-3840. PMID: 29084830; PMCID: PMC5654387.

[34] Taagaard M, Rode L, de Wolff MG, Damm P, Hagen CP, Fisher MB, Hegaard HK, Rom AL. Paracetamol use prior to and in early pregnancy: Prevalence and patterns among women with and without chronic medical diseases. Br J Clin Pharmacol. 2023 Aug;89(8):2582-2591. doi: 10.1111/bcp.15732. Epub 2023 Apr 18. PMID: 37016498.

use it during pregnancy. For these reasons, considering maternal use of acetaminophen before or after pregnancy is not a proper negative control.

C. Sensitivity Analysis

Sensitivity analysis is another technique used to assess the impact of unmeasured confounding on an observed association. One approach to conducting a sensitivity analysis is to determine how strongly an unmeasured confounder would have to be associated with the exposure and the outcome in order to explain away the observed association. Often, this involves specifying the strength of the effect of the unmeasured confounders on the exposure and on the outcome, and then determining what the true effect of the exposure on the outcome would be in the presence of the unmeasured confounder. A sensitivity analysis also can be done through a process of progressive adjustment by groups of covariates to test which of them have greater influences on the observed association. However, sensitivity analysis techniques often make assumptions, for example, that the unmeasured confounder is binary or that only one confounder exists. This can diminish the effectiveness of this technique.[35]

A meta-analysis using this technique to assess seven cohort studies regarding maternal acetaminophen use and childhood ADHD, reported that a confounder with a risk estimate of 1.69 would reduce to 10% the proportion of studies with a true effect size of RR > 1.10. In other words, performing a sensitivity analysis revealed that 90% of the studies would have a true effect size of RR < 1.10.[36] Similarly, Tronnes et al. 2020, state that "sensitivity analyses indicated that unmeasured confounding plays an important role and we cannot rule out chance or unmeasured confounding as possible explanations for our findings."[37] Although several studies reported no change in association after performing sensitivity analyses, the variables considered by the studies differ and the conclusions cannot be considered definitive with respect to control for specific confounders.

---

[35] Groenwald RH, Sterne J, Lawlor D et al. Sensitivity analysis for the effects of multiple unmeasured confounders. Annals of Epi 2016: 605-611; McGowan L. Sensitivity analysis for unmeasured confounders. Current Epidemiology Reports (2022) 9:361–375.

[36] Masarwa R, Platt RW, Filion KB. Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: A causal association or bias? Paediatr Perinat Epidemiol. 2020;34(3):309-317. doi:10.1111/ppe.12615.

[37] Trønnes JN, Wood M, Lupattelli A, Ystrom E, Nordeng H. Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children. Paediatr Perinat Epidemiol. 2020;34(3):247-256. doi:10.1111/ppe.12568.

VI. AUTISM SPECTRUM DISORDER

Turning to the epidemiologic literature on the outcomes of interest, I first examine the studies addressing the posited relationship between maternal use of acetaminophen and ASD. I begin by addressing the known and suspected risk factors for ASD, including genetics, family psychiatric history and infection and fever. I then address the relatively few studies that have focused on ASD diagnosis specifically, as well as the studies and meta-analyses on which the plaintiffs' experts rely, that have looked at various supposed proxy endpoints. Finally, I explain that the literature fails to report a clear-cut association that is necessary to justify a causation inquiry, and, alternatively, explain why a Bradford Hill analysis does not support a causal inference.

A. Background And Risk Factors

ASD is a lifelong disorder that impacts socio-communicative development and often features repetitive patterns of behavior. It occurs in about 1.6% of the population, and is diagnosed approximately four times more frequently in males than in females. Co-morbid intellectual disability is found in about 25-50% of cases depending on the methodology,[38] but many other children with ASD have average or above-average IQs. As discussed below, by far the strongest risk factors for ASD are genetic, but some potential environmental factors have been identified as well.

1. Genetic Factors

Research has shown that genetics are the predominant cause of ASD. Recently, large-scale twin studies have reported that the heritability of ASD—in other words the percentage of ASD cases attributable to inherited genetic factors-rather than either environmental factors or random chance—ranges from 80 to 90%.[39]

---

[38] Anagnostou E, Zwaigenbaum L, Szatmari P, et al. Autism spectrum disorder: advances in evidence-based practice.CMAJ 2014; 186: 509–19.

Maenner MJ, Shaw KA, Bakian AV, et al. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2018. MMWR Surveill Summ 2021;70(No. SS-11):1–16.

Khachadourian V, Mahjani B, Sandin S, Kolevzon A, Buxbaum JD, Reichenberg A, Janecka M. Comorbidities in autism spectrum disorder and their etiologies. Transl Psychiatry. 2023 Feb 25;13(1):71. doi: 10.1038/s41398-023-02374-w. PMID: 36841830; PMCID: PMC9958310.

[39] Tick B, Bolton P, Happe F, Rutter M, Rijsdijk F. Heritabilityof autism spectrum disorders: a meta-analysis oftwin studies. J Child Psychol Psychiatry 2016; 57: 585-95.

The effect of the high heritability of ASD is apparent from siblings. Twin and family studies demonstrate greater concordance for identical twins (who share an identical genetic makeup as well as the same in utero environment) as compared to non-identical twins (who share just 50% of their genetic makeup as well as the same in utero environment).[40] Still, any sibling of a child with ASD has a risk of developing the disorder 10 to 20 times greater than the general population.[41] Similar patterns are apparent for what is known as the broader autism phenotype—milder characteristics like social impairment that are related to those that define cases that meet the gold standard criteria for a diagnosis of ASD. For this phenotype, the concordance rate[42] for identical twins is 85-90% and for non-identical twins, the concordance rate is approximately 10%, which still well-exceeds the general population.[43]

Approximately 50% of the genetic etiology of ASD can be explained by the accumulation of common variants that, individually, will not cause ASD. Approximately 35% is attributable to

---

Taylor MJ, Rosenqvist MA, Larsson H, Gillberg C, D'Onofrio BM, Lichtenstein P, Lundström S. Etiology of Autism Spectrum Disorders and Autistic Traits Over Time. JAMA Psychiatry. 2020 Sep 1;77(9):936-943. doi: 10.1001/jamapsychiatry.2020.0680. PMID: 32374377; PMCID: PMC7203675.

[40] Taylor MJ, Rosenqvist MA, Larsson H, Gillberg C, D'Onofrio BM, Lichtenstein P, Lundström S. Etiology of Autism Spectrum Disorders and Autistic Traits Over Time. JAMA Psychiatry. 2020 Sep 1;77(9):936-943. doi: 10.1001/jamapsychiatry.2020.0680. PMID: 32374377; PMCID: PMC7203675.

Yirmiya N, Shaked M. Psychiatric disorders in parents of children with autism: a meta-analysis. J Child Psychol Psychiatry. 2005 Jan;46(1):69-83. doi: 10.1111/j.1469-7610.2004.00334.x. PMID: 15660645.

Daniels JL, Forssen U, Hultman CM, Cnattingius S, Savitz DA, Feychting M, Sparen P. Parental psychiatric disorders associated with autism spectrum disorders in the offspring. Pediatrics. 2008 May;121(5):e1357-62. doi: 10.1542/peds.2007-2296. Erratum in: Pediatrics. 2008 Nov;122(5):1162. PMID: 18450879.

Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The familial risk of autism. JAMA 2014; 311: 1770–7.

Tick B, Bolton P, Happe F, Rutter M, Rijsdijk F. Heritability of autism spectrum disorders: a meta-analysis oftwin studies. J Child Psychol Psychiatry 2016; 57: 585-95.

Xie S, Karlsson H, Dalman C, Widman L, Rai D, Gardner RM, Magnusson C, Schendel DE, Newschaffer CJ, Lee BK. Family History of Mental and Neurological Disorders and Risk of Autism. JAMA Netw Open. 2019 Mar 1;2(3):e190154. doi: 10.1001/jamanetworkopen.2019.0154. PMID: 30821823; PMCID: PMC6484646..

[41] Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The familial risk of autism. JAMA 2014; 311: 1770–7.

[42] Concordance rate is defined by the American Psychological Association's Dictionary of Psychology as "the percentage of pairs of twins or other blood relatives who exhibit a particular trait or disorder." https://dictionary.apa.org/concordance-rate.

[43] Hallmayer J, Cleveland S, Torres A, et al. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry 2011; 68: 1095– 102.

Tick B, Bolton P, Happe F, Rutter M, Rijsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. J Child Psychol Psychiatry 2016; 57: 585-95.

rare, inherited variants or mutations. The remaining 15% is attributable to de novo mutations—mutations that arise either spontaneously either in the child or in a parental gamete—and are not shared by the mother or father.[44]

2. Psychiatric History

There is a strong and consistent body of literature supporting the role of parental/familial psychiatric history as a risk for ASD in offspring. This reflects the risks associated with inherited genetic mutations. Epidemiologic studies report that children with ASD have a greater likelihood of having a family history of schizophrenia, depressive disorder, bipolar disorder, and personality disorders.[45] For instance, one case-control study across three separate samples from Sweden and

---

[44] Fu JM et al. Rare coding variation provides insight into the genetic architecture and phenotypic context of autism. Nat Genet. 2022 Sep;54(9):1320-1331. doi: 10.1038/s41588-022-01104-0. Epub 2022 Aug 18. PMID: 35982160; PMCID: PMC9653013.

Zhou X, Feliciano P, Shu C, Wang T, Astrovskaya I, Hall JB, Obiajulu JU, Wright JR, Murali SC, Xu SX, Brueggeman L, Thomas TR, Marchenko O, Fleisch C, Barns SD, Snyder LG, Han B, Chang TS, Turner TN, Harvey WT, Nishida A, O'Roak BJ, Geschwind DH; SPARK Consortium; Michaelson JJ, Volfovsky N, Eichler EE, Shen Y, Chung WK. Integrating de novo and inherited variants in 42,607 autism cases identifies mutations in new moderate-risk genes. Nat Genet. 2022 Sep;54(9):1305-1319. doi: 10.1038/s41588-022-01148-2. Epub 2022 Aug 18. PMID: 35982159; PMCID: PMC9470534.Klei L., McClain L. L., Mahjani B., Panayidou K., de Rubeis S., Grahnat A. C. S., et al.. (2021). How rare and common risk variation jointly affect liability for autism spectrum disorder. Mol. Autism 12, 1–13.

Grove J., Ripke S., Als T. D., Mattheisen M., Walters R. K., Won H., et al. (2019). Identification of common genetic risk variants for autism spectrum disorder. Nat. Genet. 51, 431–444.

Gaugler T, Klei L, Sanders SJ, Bodea CA, Goldberg AP, Lee AB, Mahajan M, Manaa D, Pawitan Y, Reichert J, Ripke S, Sandin S, Sklar P, Svantesson O, Reichenberg A, Hultman CM, Devlin B, Roeder K, Buxbaum JD. Most genetic risk for autism resides with common variation. Nat Genet. 2014 Aug;46(8):881-5. doi: 10.1038/ng.3039. Epub 2014 Jul 20. PMID: 25038753; PMCID: PMC4137411.

[45] Chen MH, Pan TL, Wang PW, et al. Prenatal Exposure to Acetaminophen and the Risk of Attention-Deficit/Hyperactivity Disorder: A Nationwide Study in Taiwan. J Clin Psychiatry. Published online 2019:7;

Daniels JL, Forssen U, Hultman CM, Cnattingius S, Savitz DA, Feychting M, Sparen P. Parental psychiatric disorders associated with autism spectrum disorders in the offspring. Pediatrics. 2008 May;121(5):e1357-62. doi: 10.1542/peds.2007-2296. Erratum in: Pediatrics. 2008 Nov;122(5):1162. PMID: 18450879.

Jokarinta E, Brown A, Hanimaa M et al., Parental psychiatric disorders and autism spectrum disorders Psychiatry Res. 2013 May 30; 207(3): 203–211.; Sullivan F, Magnusson C, Reichenberg A et al. Family History of Schizophrenia and Bipolar Disorder as Risk Factors for Autism. Arch Gen Psychiatry. 2012;69(11):1099-1103.

Fairthorne J, Hammond G, Bourke J, de Klerk N, Leonard H. Maternal Psychiatric Disorder and the Risk of Autism Spectrum Disorder or Intellectual Disability in Subsequent Offspring. J Autism Dev Disord. 2016;46:523-33.

Hisle-Gorman E, Susi A, Stokes T, Gorman G, Erdie-Lalena C, Nylund CM. Prenatal, perinatal, and neonatal risk factors of autism spectrum disorder. Pediatr Res. 2018 Aug;84(2):190-198. doi: 10.1038/pr.2018.23. Epub 2018 Apr 18. PMID: 29538366.

Yu T, Chang K, Kuo P. Paternal and maternal psychiatric disorders associated with offspring autism spectrum disorders: A case-control study. J Psych Res 2022 151:469-475.

Israel, showed a significant increase in ASD risk among children whose first-degree relatives (i.e., parents or siblings) had schizophrenia and bipolar disorder.[46] Similarly, a Danish study found that schizophrenia-like psychosis and affective disorder in parents were among the strongest risk factors for ASD.[47] And a meta-analysis found that both mothers and fathers of children with ASD showed consistently higher rates of anxiety disorder, social phobia, depression, and obsessive behavior.[48] The closer the relative (and therefore the more shared genes) the stronger the association, as a recent study of first-degree through fourth-degree relatives confirmed.[49]

3. Infection, Fever, And Immune Function

Epidemiological research has found associations between maternal fever and infection (including viral, bacterial, and parasitic infections) during pregnancy and increased risk of ASD.[50] However, careful research has demonstrated that the association for infection may be due to unmeasured genetic confounding, e.g., how the individual's immune system responds to an infection.

---

[46] Sullivan F, Magnusson C, Reichenberg A et al. Family History of Schizophrenia and Bipolar Disorder as Risk Factors for Autism. Arch Gen Psychiatry. 2012;69(11):1099-1103

[47] Larsson JH, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, et al. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiology 2005;161:916–25.

[48] Yirmiya N, Shaked M. Psychiatric disorders in parents of children with autism: a meta-analysis. J Child Psychol Psychiatry. 2005 Jan;46(1):69-83. doi: 10.1111/j.1469-7610.2004.00334.x. PMID: 15660645.;

Daniels JL, Forssen U, Hultman CM, Cnattingius S, Savitz DA, Feychting M, Sparen P. Parental psychiatric disorders associated with autism spectrum disorders in the offspring. Pediatrics. 2008 May;121(5):e1357-62. doi: 10.1542/peds.2007-2296. Erratum in: Pediatrics. 2008 Nov;122(5):1162. PMID: 18450879.

[49] Xie S, Karlsson H, Dalman C, Widman L, Rai D, Gardner RM, Magnusson C, Schendel DE, Newschaffer CJ, Lee BK. Family History of Mental and Neurological Disorders and Risk of Autism. JAMA Netw Open. 2019 Mar 1;2(3):e190154. doi: 10.1001/jamanetworkopen.2019.0154. PMID: 30821823; PMCID: PMC6484646.

[50] Ataldóttir HÓ, Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, et al. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. J Autism Dev Disord 2010;40:1423–30.;

Ataldóttir HÓ, Henriksen TB, Schendel DE, Parner ET. Autism after infection, febrile episodes, and antibiotic use during pregnancy: an exploratory study. Pediatrics 2012;130:e1447–554. [PubMed: 23147969];

Lee BK, Magnusson C, Gardner RM, Blomström Å, Newschaffer CJ, Burstyn I, et al. Maternal hospitalization with infection during pregnancy and risk of autism spectrum disorders. Brain Behav Immun 2015;44:100–5. [PubMed: 25218900];

Zerbo O, Iosif AM, Walker C, Ozonoff S, Hansen RL, Hertz-Picciotto I. Is maternal influenza or fever during pregnancy associated with autism or developmental delays? Results from the CHARGE (CHildhood Autism Risks from Genetics and Environment) Study. J Autism Dev Disord 2013;43:25–33. [PubMed: 22562209].

Brynge et al. 2022[51] conducted a survival analysis to examine the association between inpatient and outpatient care for any infection during pregnancy, and the likelihood of autism or intellectual disability in the child. The study used both a sibling control design and maternal pre-pregnancy fever as a purported negative control. Even after adjusting for known confounders, maternal infection during pregnancy was associated with ASD (HR=1.16, 95% CI 1.09, 1.23). However, when the authors used a sibling control to partially control for shared genetics, the association disappeared. (HR=0.94, 95% CI 0.82, 1.08). As the authors summed up their conclusions: "although infections in pregnant women are associated with . . . autism . . . in their children, the association . . . does not appear to reflect a causal relationship, but is more likely to be explained by factors shared between family members such as genetic variation."

Of course, regardless of whether fever or infection are independent causes of ASD or whether they are signals for unmeasured genetic confounding, their well-established association with the disorder substantially complicates any effort to suggest a relationship between acetaminophen and ASD. Acetaminophen is widely used to treat fever and is the most common such medication for pregnant women, which presents the possibility of confounding by indication.

4. Prenatal And Obstetric Factors

Because ASD is considered to be congenital (present at birth), there have been numerous studies of the association between various prenatal and obstetric factors and the risk of ASD in offspring. Some of these risk factors are well-established, such as low birthweight or premature birth (discussed in further detail in subsection 6 below) and neonatal brain hemorrhage. Other obstetric factors are less well-established, including low Apgar scores, uterine bleeding, parity, respiratory distress, hyperbilirubinemia, meconium staining, breech presentation, and interpregnancy interval (IPI). Although these factors have been identified in one or more studies as significantly increasing the risk of ASD, the evidence is still sparse or mixed, and further evaluation is needed.[52] Because of the low incidence of any particular risk factor, they are often

[51] Brynge M, Sjöqvist H, Gardner RM, Lee BK, Dalman C, Karlsson H. Maternal infection during pregnancy and likelihood of autism and intellectual disability in children in Sweden: a negative control and sibling comparison cohort study. Lancet Psychiatry. 2022 Oct;9(10):782-791. doi: 10.1016/S2215-0366(22)00264-4. Epub 2022 Sep 7. PMID: 36087610.

[52] Burd L, Severud R, Kerbeshian J, Klug MG. Prenatal and perinatal risk factors for autism. J Perinat Med. 1999;27(6):441–450.

Gillberg C, Gillberg IC. Infantile autism: a total population study of reduced optimality in the pre-, peri-, and neonatal period. J Autism Dev Disord. 1983;13(2):153–166.

combined into an optimality score. The flaw with such a score is that it lacks specificity, rendering the results less compelling. Despite the limited evidence available, the possibility that these factors could be associated with (or even, in some cases, increase the risk of) ASD means that a well-designed epidemiological study should control for them as potential confounders.

5. Parental Age

Advanced parental age is a well-established risk factor for ASD, likely because of the increased number of opportunities for mutations.[53] Maternal age is independently associated with

---

Lord C, Mulloy C, Wendelboe M, Schopler E. Pre- and perinatal factors in high-functioning females and males with autism. J Autism Dev Disord. 1991;21(2):197–209.

Bryson SE, Smith IM, Eastwood D. Obstetrical suboptimality in autistic children. J Am Acad Child Adolesc Psychiatry. 1988;27(4): 418–422.

Finegan J, Quarrington B. Pre-, peri-, and neonatal factors and infantile autism. J Child Psychol Psychiatry. 1979;20(2):119–128.

Piven J, Simon J, Chase GA, et al. The etiology of autism: pre-, peri- and neonatal factors. J Am Acad Child Adolesc Psychiatry. 1993;32(6):1256–1263.

Larsson HJ, Eaton WW, Madsen KM, et al. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol. 2004;161(10):916–925.

Deykin EY, MacMahon B. Pregnancy, delivery, and neonatal complications among autistic children. Am J Dis Child. 1980; 134(9):860–864.

Levy S, Zoltak B, Saelens T. A comparison of obstetrical records of autistic and nonautistic referrals for psychoeducational evaluations. J Autism Dev Disord. 1988;18(4):573–581.

Mason-Brothers A, Ritvo ER, Pingree C, et al. The UCLA University of Utah epidemiologic survey of autism: prenatal, perinatal, and postnatal factors. Pediatrics. 1990;86(4):514–519.

Juul-Dam N, Townsend J, Courchesne E. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder- not otherwise specified, and the general population. Pediatrics. 2001;107(4).

Hultman CM, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. Epidemiology. 2002;13(4):417–423.

[53] Croen LA, Najjar DV, Fireman B, Grether JK. Maternal and paternal age and risk of autism spectrum disorders. Arch Pediatr Adolesc Med 2007;161(4):334–40.

Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. Br J Psychiatry. 2009 Jul;195(1):7-14. doi: 10.1192/bjp.bp.108.051672. PMID: 19567888; PMCID: PMC3712619.

Shelton JF, Tancredi DJ, Hertz-Picciotto I. Independent and dependent contributions of advanced maternal and paternal ages to autism risk. Autism Res. 2010 Feb;3(1):30-9. doi: 10.1002/aur.116. Erratum in: Autism Res. 2010 Apr;3(2):98. PMID: 20143326; PMCID: PMC4068119.

Sandin et al. The heritability of ASD. JAMA 2017; 318: 97:417–423.

Lyall K, Song L, Botteron K, Croen LA, Dager SR, Fallin MD, Hazlett HC, Kauffman E, Landa R, Ladd-Acosta C, Messinger DS, Ozonoff S, Pandey J, Piven J, Schmidt RJ, Schultz RT, Stone WL, Newschaffer CJ, Volk HE. The Association Between Parental Age and Autism-Related Outcomes in Children at High Familial Risk for Autism. Autism Res. 2020 Jun;13(6):998-1010. Doi: 10.1002/aur.2303. Epub 2020 Apr 21. PMID: 32314879; PMCID: PMC7396152.

ASD in several studies.[54] A population-based cohort study in Sweden of advanced paternal age and the association of increased risk of ASD reported a 76% increased risk for ASD in children whose fathers were older than 45 years old compared to children of fathers 20–25 years old (HR=1.76, 95% CI 1.36, 2.28).[55] A meta- analysis of 27 studies found the highest parental age category was associated with an increased risk of ASD in the offspring, with aOR=1.41 (95% CI 1.29, 1.55) for mothers and aOR=1.55 (95% CI 1.39, 1.73) for fathers.[56] In addition, a large cohort study with data from five countries reported that both advanced paternal and maternal age were independently associated with increased risk of ASD after adjusting for confounding and the other parent's age.[57]

6. Low Birthweight And Gestational Age

There is a strong body of literature supporting the association between low birthweight and pre-term birth and an increased risk of ASD, including my own study on the prevalence of ASD in a low birthweight cohort.[58] Other studies have likewise found that both gestational age[59] and low birthweight[60] (≤2.5 kg (approximately 5.5 lbs.)) are associated with ASD. And a recent study from South Korea found a type of dose-response with infants weighing 1.5-1.9 kg (approximately 3.3-4.2 lbs) more likely to develop ASD than those from 2.0-2.4 kg (4.4-5.3 lbs).[61]

---

[54] Croen LA, Najjar DV, Fireman B, Grether JK. Maternal and paternal age and risk of autism spectrum disorders. Arch Pediatr Adolesc Med 2007;161(4):334–40.

Sandin et al. The heritability of ASD. JAMA 2017; 318: 97:417–423.

[55] D'Onofrio BM, Rickert ME, Frans E, Kuja-Halkola R, Almqvist C, Sjölander A, et al.Paternal age at childbearing and offspring psychiatric and academic morbidity. JAMA Psychiatry 2014;71(4):432–8.

[56] Wu S, Wu F, Ding Y, Hou J, Bi J, Zhang Z. Advanced parental age and autism risk in children: a systematic review and meta-analysis. Acta Psychiatr Scand. 2017 Jan;135(1):29-41. Doi: 10.1111/acps.12666. Epub 2016 Nov 14. PMID: 27858958.

[57] Sandin et al The heritability of ASD. JAMA 2017; 318: 97:417–423.

[58] Pinto-Martin JA, Levy SE, Feldman JF, Lorenz JM, Paneth N, Whitaker AH. Prevalence of autism spectrum disorder in adolescents born weighing <2000 grams. Pediatrics. 2011 Nov;128(5):883-91. Doi: 10.1542/peds.2010-2846. Epub 2011 Oct 17. PMID: 22007018; PMCID: PMC3208957.

[59] D'Onofrio BM, Rickert ME, Frans E, Kuja-Halkola R, Almqvist C, Sjölander A, et al. Paternal age at childbearing and offspring psychiatric and academic morbidity. JAMA Psychiatry 2014;71(4):432–8.

[60] Lampi KM, Lehtonen L, Tran PL, Suominen A, Lehti V, Banerjee PN, Gissler M, Brown AS, Sourander A. Risk of autism spectrum disorders in low birth weight and small for gestational age infants. J Pediatr. 2012 Nov;161(5):830-6. Doi: 10.1016/j.jpeds.2012.04.058. Epub 2012 Jun 5. PMID: 22677565; PMCID: PMC3449022.

[61] Song P, Zha M, Yang Q, Zhang Y, Li X, Rudan I. The prevalence of adult attention-deficit hyperactivity disorder: A global systematic review and meta-analysis. J Glob Health. 2021;11:04009.

7. Maternal Obesity

Maternal obesity during pregnancy appears to be associated with ASD in children.[62] However, this association, much like the association with infection, appears likely to be the result of residual genetic confounding, with one study showing a statistically significant near-doubling of risk (maOR=1.94, 95% CI 1.72-2.17) attenuated to insignificance after application of a sibling control (maOR=1.06, 95% CI 0.75-1.50).[63]

8. Maternal Stress

A growing body of evidence from a wide variety of studies suggests an association between maternal stress and ASD.[64] A recent study (Beversdorf et al. 2019) describes the evidence supporting the contribution of maternal stress to ASD risk and the mechanism by which it might operate.[65] However, assessment of stress is challenging and vulnerable to information bias and recall bias, which could skew the results. Therefore, it is premature to claim stress is an established risk factor. Still, given that an association has been repeatedly demonstrated and the possibility that stress could be associated with medication use, studies should account for this potential confounding factor.

---

[62] Li YM, Ou JJ, Liu L, Zhang D, Zhao JP, Tang SY. Association Between Maternal Obesity and Autism Spectrum Disorder in Offspring: A Meta-analysis. J Autism Dev Disord. 2016 Jan;46(1):95-102. Doi: 10.1007/s10803-015-2549-8. PMID: 26254893.

[63] Gardner RM, Lee BK, Magnusson C, Rai D, Frisell T, Karlsson H, Idring S, Dalman C. Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: Results from a Swedish total population and discordant sibling study. International Journal of Epidemiology. 2015;44(3):870-83.

[64] Larsson JH, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, et al. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiology 2005;161:916–25.

Beversdorf DQ, Manning SE, Hillier A, Anderson SL, Nordgren RE, Walters SE, et al. Timing of prenatal stressors and autism. J Autism Dev Disord 2005;35:471–8.

Kinney DK, Miller AM, Crowley DJ, Huang E, Gerber E. Autism prevalence following prenatal exposure to hurricanes and tropical storms in Louisiana. J Autism Devel Disord 2008;28:481–8.

Roberts AL, Lyall K, Rich-Edwards JW, Ascherio A, Weisskopf MG. Maternal exposure to childhood abuse is associated with elevated risk of autism. JAMA-Psychiatry 2013;70:508–15; Class QA,

Abel KM, Khashan AS, Rickert ME, Dalman C, Larsson H, et al. Offspring psychopathology following preconception, prenatal and postnatal maternal bereavement stress. Psychol Med 2014;44:71–84.

Roberts AL, Lyall K, Rich-Edwards JW, Ascherio A, Weisskopf MG. Maternal exposure to intimate partner abuse before birth is associated with risk of autism spectrum disorder in offspring. Autism 2016;20: 26–36.

[65] Beversdorf DQ, Stevens HE, Margolis KG, Van de Water J. Prenatal Stress and Maternal Immune Dysregulation in Autism Spectrum Disorders: Potential Points for Intervention. Curr Pharm Des. 2019;25(41):4331-4343. Doi: 10.2174/1381612825666191119093335. PMID: 31742491; PMCID: PMC7100710.

9. Valproic Acid

Exposure to valproic acid in utero through maternal use is associated with increased risk of ASD. Valproate is indicated for the treatment of epilepsy, manic episodes associated with bipolar disorder, and prophylaxis of migraine headaches. In one study using ASD diagnosis found in children's medical records, even after adjusting for potential confounding factors (including the obvious ones such as psychiatric history and seizure severity), maternal use of valproic acid was associated with a statistically significant more than doubling of ASD risk.[66] The data establishing the association between ASD and valproic acid is considerably more robust than the data on prenatal acetaminophen exposure. The association is stronger and more consistent, and researchers have much more precise information on exposure. Because valproate is a prescription medication given for a clear medical diagnosis in the mother, data on timing, dose and duration of exposure is readily available from medical records.

B. Overview Of Epidemiological Data Addressing Prenatal Exposure To Acetaminophen And ASD

Several studies have attempted to evaluate the association between in utero acetaminophen exposure and either ASD or various tests, symptoms, and tools thought to be related to ASD or to the broader autism phenotype. Of those, only five assessed the association between maternal use of acetaminophen and clinical diagnoses of ASD in children. That includes three cohort studies that specifically set out to investigate the issue (Liew et al. 2016c, Ji et al. 2018, and Ji et al. 2020) and one cohort study limited to febrile women (Hornig et al. 2018). It also includes one retrospective case-control study (Saunders et al. 2019).

In addition to these studies of diagnosed ASD, several other studies have evaluated the association between in utero acetaminophen exposure and a wide variety of behavioral outcomes, as defined by various different screening tools. These, too, have produced inconsistent results. Efforts have been made at meta-analyses, but the outcomes across various studies are too

---

[66] Wiggs KK, Rickert ME, Hernandez-Diaz S, Bateman BT, Almqvist C, Larsson H, Lichtenstein P, Oberg AS, D'Onofrio BM. A Family-Based Study of the Association Between Labor Induction and Offspring Attention-Deficit Hyperactivity Disorder and Low Academic Achievement. Behav Genet. 2017 Jul;47(4):383-393. doi: 10.1007/s10519-017-9852-4. Epub 2017 May 27. PMID: 28551761.

Christensen J, Grønborg T, Sørensen M et al. Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA. 2013 April 24; 309(16): 1696–1703.

heterogeneous to be meaningfully meta-analyzed, as the most recent effort to perform one concluded.[67]

Overall, the body of literature does not support the conclusion that in utero acetaminophen exposure causes ASD.

1. Studies Addressing ASD As An Endpoint

The following table summarizes the five studies that have addressed whether in utero acetaminophen exposure increases the risk of ASD diagnosis.

Three of the five studies weigh against plaintiffs' hypothesis, and the two studies that arguably support their positions each have substantial limitations that call their results into serious question. Specifically, Ji et al. 2018 and Saunders et al. 2019 show no statistically significant association between exposure and ASD. Hornig et al. 2018, which found acetaminophen protective in cases of fever further cuts against plaintiffs' hypothesis, although the applicability of that study to afebrile women is unknown. One study (Liew et al. 2016c) suggested a weak association for some forms of ASD but not for others. And one study (Ji et al. 2020) suggested a somewhat stronger association, but it expressly acknowledged that its findings were likely limited to peripartum (i.e., during childbirth) exposure (which is a different question from the one addressed in the bulk of the studies) and also has several other flaws and limitations.

Study	Population	Exposure Measurement	Outcomes Tested	Results
Liew et al. 2016c	64,322 children from Danish National Birth Cohort	Maternal self-report at 12 & 30 weeks gestation & 6 mos. post-partum	ASD, ASD with co-occurring hyperkinetic disorder	ASD: aHR = 1.19, 95% CI 1.04-1.35
				Infantile autism: aHR = 1.10, 95% CI 0.89-1.37
				ASD w/ HKD: aHR = 1.51, 95% CI 1.19-1.92
				ASD w/o HKD: aHR = 1.07, 95% CI 0.92-1.24
				Infantile w/ HKD: aHR = 1.55, 95% CI 0.98-2.45

[67] Ricci C, Albanese C, Pablo L In utero acetaminophen exposure and child neurodevelopmental outcomes: Systematic review and meta-analysis Paediatr Perinat Epidemiol. 2023;00:1–12.

Study	Population	Exposure Measurement	Outcomes Tested	Results
				Infantile w/o HKD: aHR = 0.98, 95% CI 0.77, 1.26
Hornig et al. 2018	113,607 children from Norwegian Mother and Child Cohort Study	Maternal self-report	ASD	Risk associated with fever: 2nd trimester aOR = 1.40, 95% CI 1.09-1.79 2nd trimester with acetaminophen use aOR = 1.37, 95% CI 0.98-1.90 2nd trimester without acetaminophen use aOR = 1.44, 95% CI 1.02-2.03
Ji et al. 2018	1,180 mother/infant pairs from Boston Birth Cohort (BBC).	Acetaminophen metabolites in maternal blood plasma 1-3 days post-partum	ASD, ADHD, other developmental disorder	Total acetaminophen burden: aOR=1.39, 95% CI 0.59-3.27 No association in any of 48 calculated ORs
Saunders et al. 2019	141 cases, 199 age/sex-matched controls from Atlantic Canada	Maternal self-report at 0-10 years post-partum	maternal-reported ASD diagnosis	Pearson Chi-Square: 1.612; p-value: 0.657
Ji et al. 2020	996 children from BBC	Acetaminophen metabolites in umbilical cord plasma	ASD, ADHD	Cord acetaminophen burden: Second tertile: OR=2.14, 95% CI 0.93-5.13; Third tertile: OR=3.62, 95% CI 1.62-8.60

These five studies are discussed in more detail below.

Ji et al. 2018.[68] Ji and colleagues followed 1,180 infants from the Boston Birth Cohort, a sample from one large urban hospital. The authors obtained data on ASD diagnosis (as well as diagnosis with ADHD and other developmental disorders) from electronic health records. Maternal acetaminophen use was evaluated based on samples of blood plasma taken from mothers 1-3 days post-partum. The blood was sampled for unchanged acetaminophen, and its metabolites acetaminophen glucuronide, and 3-(*N*-Acetyl-L-cystein-*S*-yl) acetaminophen. The authors calculated a "total acetaminophen burden" "by combining all of the acetaminophen metabolites levels with a weighing of their proportions in the acetaminophen metabolic pathway[.]" This method of measuring acetaminophen exposure has the advantage of being objective and precise, unlike asking mothers. But it has the major disadvantage of only being able to measure exposure at a single point in time—here, 1-3 days after delivery. That is because acetaminophen and its metabolites dissipate quickly—with acetaminophen itself having a half-life of just 1.5-3 hours.[69]

The authors calculated associations between ASD and each acetaminophen metabolite as well as total acetaminophen burden. They calculated different levels of each metabolite and total burden, and they adjusted for a series of different covariates. All in all, they calculated 48 odds ratios and confidence intervals and not a single one produced a statistically significant association between acetaminophen exposure and ASD. For example, in the most full adjusted model, those with detectable but below median exposure had an aOR of 1.43, and a 95% CI from 0.64-3.15, with a p-value of 0.382, while those with above-median detective exposure had an aOR of 1.39, a 95% CI from 0.59-3.27, and a p-value of 0.456. The authors summarized their results clearly: "the risks of ASD diagnosis . . . were not significantly associated with maternal plasma levels of acetaminophen exposure across all models."

The Ji study had limitations. The most significant has already been mentioned. As the study authors acknowledge, the "one time measurement" could only account for "recent use"—likely in the peripartum period (e.g, during labor). The authors suggest that "women with detectable levels of acetaminophen biomarkers are likely to be more regular users." But that is

---

[68] Ji Y, Riley AW, Lee LC, et al. Maternal Biomarkers of Acetaminophen Use and Offspring Attention Deficit Hyperactivity Disorder. Brain Sci. 2018;8(127):15. Doi:doi:10.3390/brainsci8070127.

[69] Liu DJ, Collaku A. Bioequivalence and Safety of Twice-Daily Sustained-Release Paracetamol (Acetaminophen) Compared With 3- and 4-Times-Daily Paracetamol: A Repeat-Dose, Crossover Pharmacokinetic Study in Healthy Volunteers. Clin Pharmacol Drug Dev. 2018 Jan;7(1):77-86. doi: 10.1002/cpdd.369. Epub 2017 Aug 16. PMID: 28815997; PMCID: PMC6084369.

speculative, especially in light of the fact that labor brings on pain and discomfort that is unique to that moment in the pregnancy and often prompts pain-management interventions that are not used at any other time during pregnancy (e.g., the use of a local anesthetic). Other flaws in the study include the fact that despite six different covariant models, none of them sought to account for genetic or familial confounding. However, this may be less of a limitation given the result because in other studies, adjustments for confounding have generally moved the results toward null rather than away from null, suggesting that such adjustments would have further attenuated the results. The study also tested a series of different metabolites and dosage levels, which raises the possibility of random error absent multiplicity adjustment, but again that would lead to the overreporting of statistically significant results, not to their absence. Finally, although the authors sought to group acetaminophen by "tertiles" (i.e., thirds) and to stratify the acetaminophen metabolites by above- and below-median levels, it is unclear exactly how those groupings correspond to dose exposure.

Notably, Dr. Baccarelli and other plaintiffs' experts ignore this study. Both Drs. Baccarelli and Cabrera do cite Ji's very similar study from the same cohort two years later, which is subject to all the same limitations.[70] While Dr. Cabrera cites Ji et al. 2018 to suggest that there is an association between acetaminophen and ADHD, he ignores the portion of the study that reports no association between maternal acetaminophen use and childhood ASD.[71] This omission raises the possibility of bias in his review of the literature and does not reflect a thorough and objective review of the epidemiologic data on the association between acetaminophen and ADHD and ASD.

Dr. Baccarelli justifies this approach—which certainly appears results-oriented—by claiming that because "the two papers involved the same data and results," he can evaluate only "the most recent of the two."[72] That assertion demonstrates an incomplete review of the data. The two studies are certainly similar, but they test different samples, one of maternal plasma and one of umbilical cord plasma. More importantly, the results are diametrically opposed: the later study suggest an association between acetaminophen and ASD while this study does not.

[70] Baccarelli Rep. at 101-103; Expert Report of Robert M. Cabrera, Ph.D ("Cabrera Rep.") at 140.

[71] Cabrera Rep. at 140.

[72] Baccarelli Rep. at 103.

Saunders et al. 2019.[73] Saunders and colleagues performed a case-control study "focused on the presence of [various] environmental exposures during pregnancy in mothers of children diagnosed with autism spectrum disorder" using a case-control design. The ASD group consisted of 141 children age 10 and under who were diagnosed with ASD before age 6 and had no other developmental disorder or chromosomal abnormality. The control group consisted of 199 age- and sex-matched children without ASD from the "same region" of the same city in Atlantic Canada. The authors asked both groups of mothers about various environmental exposures during pregnancy, including acetaminophen use. Statistical significance was tested initially using a chi-square test. Acetaminophen was not associated with ASD at all—indeed the p-value indicates that the difference between the two groups was so small it would appear more often than not by chance even absent a true effect: χ^2=1.612, p=0.657. Because there was no significant association using the chi-square test, the authors did not calculate an odds ratio or confidence interval. Use of other medications (not including acetaminophen or antibiotics) had a statistically significant effect on ASD risk, and an odds ratio calculation suggested it likely resulted in more than doubling of the risk: χ^2=9.557, p=.002, OR=2.29; CI: 1.29-4.36. This was true of other environmental exposures like smoking (OR=2.56; CI: 1.91-5.49). In confirmation of the genetic nature of the disorder, presence of a family member with autism was also significantly associated with ASD diagnosis (OR=2.72; CI: 1.29-5.73).

The study has several limitations, but in general, those limitations would be more apt to artificially elevate any reported association as opposed to reducing it. As Dr. Baccarelli correctly points out, Saunders and colleagues do not appear to have adjusted for potential confounding factors, but as I noted above, controlling for such confounding factors in similar studies has reduced observed associations.[74] In addition, like all retrospective case-control studies, *Saunders* is subject to recall bias since women were asked about exposures that occurred several years earlier. But as discussed above, recall bias, too, ordinarily results in an overestimation of the true association between an exposure and an adverse outcome, because those who suffer an adverse outcome are more likely to assert recollection of exposure to drugs and other factors under study. Thus, recall bias is a highly unlikely explanation for the lack of association between

[73] Saunders A, Woodland J, Gander S (July 24, 2019) A Comparison of Prenatal Exposures in Children with and without a Diagnosis of Autism Spectrum Disorder. Cureus 11(7): e5223. DOI 10.7759/cureus.5223.

[74] Baccarelli Rep. at 101.

acetaminophen and ASD observed in this study, though it may have an impact on the positive associations observed with other environmental factors. Other study design issues would be more likely to lead to non-differential error, such as the fact that controls were selected entirely from a public recruitment campaign, while cases were selected from both public recruitment and medical records. In sum, while this study did have flaws, correction of at least some of them would only further attenuate any association.

Finally, I note one study, ***Hornig et al. 2018***,[75] that evaluated the potential protective effect of acetaminophen use to treat fever. This study did not directly measure the association between maternal use of acetaminophen and childhood ASD, but it did report on the effect acetaminophen had on the association between fever and childhood ASD. In this study, maternal fever was associated with a slightly increased risk of ASD across all trimesters (aOR=1.34; 95% CI 1.07-1.67), but stratification by trimester revealed that the increased risk was significant in the second trimester only (aOR=1.40; 95% CI 1.09, 1.79). The authors also reported a dose-response relationship with 3 or more fevers after 12 weeks of pregnancy (aOR=3.12; 95% CI 1.28, 7.63). In the second trimester, treatment with acetaminophen attenuated the risk of fever such that it was no longer statistically significant (untreated aOR=1.44 95% CI 1.02, 2.03; treated aOR=1.37, 95% CI 0.98, 1.90). Interestingly, treatment with ibuprofen, which has similar antipyretic properties to acetaminophen, did not reduce the risk of ASD, suggesting that the results cannot be explained by the simple fact of fever treatment.

I weigh this study only slightly in my consideration of the evidence. It is not clear whether the protective result observed can be extrapolated to afebrile women. Still, the apparent protective effect of acetaminophen, coupled with the lack of any such effect for ibuprofen, provides some additional evidence that acetaminophen use is, at the very least, not positively associated with ASD.

Two studies, Liew et al. 2016 and Ji et al. 2020, report an association between maternal acetaminophen use and at least some forms of ASD. The first suggests a very weak association between acetaminophen use and ASD, but only when ASD co-occurs with hyperkinetic disorder ("HKD" a hyperactivity disorder). The second finds an association between use at or near

[75] Hornig M, Bresnahan A, X Che X et al. Prenatal fever and autism risk. Molecular Psychiatry (2018) 23, 759–766.

childbirth and ASD, but only without co-occurring ADHD. Neither study adequately accounts for confounders, including genetic confounders.

Liew et al. 2016c.[76] Liew and colleagues followed 64,322 children and mothers from the Danish National Birth Cohort. Maternal acetaminophen use was evaluated based on phone interviews performed during pregnancy. Children's diagnoses were taken from the Danish National Hospital Registry and Danish Psychiatric Registry. The results were mixed. As compared to "never use," "ever use" of acetaminophen was associated with a very small, but statistically significant, increase in ASD risk (aHR=1.19, 95% CI 1.04, 1.35). When those risks were broken down by subtype, the results were inconsistent. The only subtype of ASD for which a statistically significant association remained was ASD with hyperkinetic disorder (aHR=1.51, 95% CI 1.19, 1.92). No significant risk was found for ASD without hyperkinetic disorder, which was the most frequently diagnosed disorder (aHR =1.07, 95% CI 0.92-1.24). Infantile autism was likewise not significantly associated with acetaminophen exposure when taken as a whole (aHR=1.10, 95% CI 0.89, 1.37) or when broken down by cases without HKD (aHR = 0.98, 95% CI 0.77, 1.26), and those with HKD (aHR =1.55, 95% CI 0.98, 2.45).

The investigators stated that "[i]f ASD and hyperkinetic disorder are considered two different disorders with different etiologies, our results can be interpreted as acetaminophen only having an impact on hyperkinetic disorder but not ASD." But they did not explain why acetaminophen would be associated with cases involving HKD, but not with other cases. And that result is inconsistent with results from Ji et al. 2020,[77] in which acetaminophen exposure did not increase the risk of ASD comorbid with ADHD (which is similar to ASD with HKD), but the authors did report an association between acetaminophen exposure and ASD without ADHD.

The weak and inconsistent association found by this study is very likely the result of residual confounding. While the authors controlled for certain environmental factors, no information on genetic risk was reported, and no effort was made to control for familial or genetic confounding. In fact, the authors acknowledged "residual confounding by indication or genetic

---

[76] Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study. Autism Res Off J Int Soc Autism Res. 2016;9(9):951-958. doi:10.1002/aur.1591.

[77] Ji Y, Azuine RE, Zhang Y, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. JAMA Psychiatry. 2020;77(2):180. doi:10.1001/jamapsychiatry.2019.3259.

factors [are] alternate explanations" for the small association reported.[78] Another possible explanation for the results is that the sheer number of variables and outcomes tested was likely to produce statistically significant results by chance. The supplementary tables reveal a large number of comparisons, and there does not appear to have been any adjustment to p-values to reduce the risk of Type I error.

In addition to the ever use/never use comparison, the authors sought to perform a dose-response analysis. Their ability to do so is questionable because the authors did not actually have data on dosage. Rather they had maternal self-reports on the number of weeks and trimesters of use, but no knowledge of the number of pills taken. As with the never/ever comparison, there was no dose response for non-hyperkinetic cases (nor could there have been given the lack of any association in the first place). Any associations for infantile autism, either with or without HKD, were not significant as measured by p-trend. As for ASD with HKD, the supplemental tables reveal a confused picture. When acetaminophen exposure was measured by trimesters, a statistically significant association was reported for boys but not girls; when exposure was measured by weeks, the association was significant for girls but not boys.[79]

Although Liew et al. 2016 provides some equivocal evidence for an association between acetaminophen exposure and one particular subtype of ASD, the association is weak, especially in light of unmeasured cofounders, and the results lack plausibility absent any reason why acetaminophen would cause one subtype of ASD but not another.

Ji et al. 2020.[80] Like the study by the same lead author from two years earlier, this one used a sample from the Boston Birth Cohort and investigated a possible association between maternal acetaminophen biomarkers and ASD and other neurodevelopmental disorders. This time, the authors sampled 996 children. Of that group, 66 had ASD without ADHD, and an additional 42 had ASD comorbid with ADHD. Of the remainder, most had either ADHD alone or other developmental disorders, and just 327 (less than a third) were neurotypical. As before, the authors

[78] Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study. Autism Res Off J Int Soc Autism Res. 2016;9(9):951-958. doi:10.1002/aur.1591.

[79] Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study. Autism Res Off J Int Soc Autism Res. 2016;9(9):951-958. doi:10.1002/aur.1591.at Supplemental Table 2.

[80] Ji Y, Azuine RE, Zhang Y, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. JAMA Psychiatry. 2020;77(2):180. doi:10.1001/jamapsychiatry.2019.3259.

recorded unchanged acetaminophen, two acetaminophen metabolites, and a self-calculated total acetaminophen burden. Unlike the findings from two years earlier, the authors found a "significant positive association between cord plasma acetaminophen metabolites and . . . the risk of ASD in childhood." Specifically, the study population was divided into thirds (tertiles) based on the amount of acetaminophen in the maternal cord blood (unlike other studies that used biomarkers to measure acetaminophen,[81] all samples contained some detectable acetaminophen levels). Because the sample sizes of affected children were quite small, the results were inexact and the confidence intervals large. With respect to ASD without ADHD, those in the second tertile had no statistically significant elevation in risk compared to those in the first (aOR=2.14, CI: 0.93-5.13), while those in the third tertile did see a significant increase in risk over the first (aOR=3.62, CI: 1.62-8.60). With respect to ASD comorbid with ADHD, neither group had a statistically significant increase (aOR 2.1; CI: 0.81-5.72 for the second tertile and aOR 2.44; CI: 0.92-6.82 for the third).[82]

This study had many of the same strengths and weakness as Ji's earlier study. It used an objective measurement of acetaminophen exposure, but one that could only evaluate exposure at or near childbirth, not during pregnancy as a whole, which the authors acknowledged: "Given that the half-life of acetaminophen in adults is less than three hours, the cord plasma measurement may at most reflect maternal use of acetaminophen at or near childbirth." Thus, it is impossible to determine exposure throughout gestation, including during the most critical periods of brain development. As before, while the results were adjusted for various environmental exposures, they were not adjusted for parental mental health or for parental or genetic risk factors. Again, the authors acknowledged this limit: "[w]e were unable to exclude the potential residual confounders because of unmeasured genetic and environmental factors." In addition, while the authors sought to control for confounding by indication (e.g., maternal fever) by electronic medical records, acetaminophen is most commonly taken over the counter, and the reason for use may not be recorded.

---

[81] Baker BH, Lugo-Candelas C, Wu H, et al. Association of Prenatal Acetaminophen Exposure Measured in Meconium With Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity. JAMA Pediatr. 2020;174(11):1073-1081. doi:10.1001/jamapediatrics.2020.3080.

Bornehag CG, Reichenberg A, Hallerback MU, et al. Prenatal exposure to acetaminophen and children's language development at 30 months. Eur Psychiatry. 2018;51:98-103. doi:10.1016/j.eurpsy.2017.10.007.

[82] Ji Y, Azuine RE, Zhang Y, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. JAMA Psychiatry. 2020;77(2):180. doi:10.1001/jamapsychiatry.2019.3259.

Some details of the study raise serious questions about the study's results. The authors acknowledged that "all cord samples had detectable unchanged acetaminophen." Because it is extremely unlikely that all 996 women had recently taken acetaminophen, this suggests some non-medicinal environmental exposure to acetaminophen that has not been accounted for or a laboratory error. Additionally, some of the results are inconsistent with Ji et al. 2018, and the reported association between acetaminophen and ASD without comorbid ADHD, contradicts the findings in Liew et al. 2016 that acetaminophen only raised the risk of ASD ***with*** hyperkinetic (i.e., hyperactive) disorder.

In sum, four studies have evaluated the association between in utero acetaminophen and diagnosed ASD. One additional study has evaluated the relationship in the contest of febrile women only. Of the five, three studies showed no statistically significant association between in utero exposure and diagnosis, two of which produced a point estimate below 1.0, suggesting that if there were any effect it would be protective. One study suggested a small, but statistically significant, association with ASD, but the result was dependent on the co-occurrence of HKD. And one suggested an association with ASD not comorbid with ADHD, only for peripartum exposure likely during the peripartum period and therefore has little-to-no bearing on use of acetaminophen throughout pregnancy. The weight of the evidence suggests no association, much less a consistent or strong one, between acetaminophen in utero and ASD.

2. Studies Addressing Other Neurobehavioral Outcome

There is an additional body of literature that looks at supposed proxies for (rather than actual diagnoses of) ASD, but these studies are very imprecise and must be viewed as hypothesis-generating only. Specificity of outcome is a hallmark of a well-designed epidemiologic study. In the absence of specificity, associations have less reliability and validity. This is particularly true when the outcome is not biologically based, as it is for outcomes such as diabetes, cancer and heart disease, because the opportunity for misclassification is enhanced. ASD diagnoses rely on clinical assessment and judgment of behavioral symptoms; thus, there is greater heterogeneity in the final outcome and the possibility of inter-rater differences. This makes it all the more important that epidemiological studies seeking to assess the relationship between prenatal acetaminophen exposure and ASD in offspring use a gold-standard diagnostic tool for ASD, rather than less rigorous forms of assessment, to determine the final outcome.

Nevertheless, plaintiffs' experts rely heavily on studies that do not involve clinically-diagnosed ASD. Because screening tools are not diagnostic but are instead used to determine if a more thorough evaluation is required,[83] the sensitivity of such instruments is intentionally high, while the specificity is low, resulting in a high likelihood of false positives.

A total of 15 such screening tools have been used, in whole or in part, as proxies for either ASD or ADHD in the literature:

(1) Ages and Stages Questionnaire (ASQ)[84]
(2) Child Behavior Checklist (CBCL)[85]
(3) Strength and Difficulties Questionnaire (SDQ)[86]

---

[83] Hyman SL, Levy SE, Myers SM; COUNCIL ON CHILDREN WITH DISABILITIES, SECTION ON DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. Pediatrics. 2020 Jan;145(1):e20193447. doi: 10.1542/peds.2019-3447. Epub 2019 Dec 16. PMID: 31843864.

[84] Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol. 2013;42(6):1702-1713. doi:10.1093/ije/dyt183.

Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MMHJ, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero : a propensity score matched cohort study. Int J Epidemiol. 2016;45(6):dyw192. doi:10.1093/ije/dyw192.

Skoglund C, Chen Q, D'Onofrio BM, Lichtenstein P, Larsson H. Familial confounding of the association between maternal smoking during pregnancy and ADHD in offspring. J Child Psychol Psychiatry. 2014;55(1):61–8.

[85] Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol. 2013;42(6):1702-1713. doi:10.1093/ije/dyt183.

Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MMHJ, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol *in utero*: a propensity score matched cohort study. *Int J Epidemiol*. 2016;45(6):dyw192. doi:10.1093/ije/dyw192.

Tovo-Rodrigues L, Schneider BC, Martins-Silva T, et al. Is intrauterine exposure to acetaminophen associated with emotional and hyperactivity problems during childhood? Findings from the 2004 Pelotas birth cohort. BMC Psychiatry. 2018;18(1):368. doi:10.1186/s12888-018-1942-1.

Sznajder KK, Teti DM, Kjerulff KH. Maternal use of acetaminophen during pregnancy and neurobehavioral problems in offspring at 3 years: A prospective cohort study. Sun K, ed. *PLOS ONE*. 2022;17(9):e0272593. doi:10.1371/journal.pone.0272593; Parker SE, Collett BR, Werler MM. Maternal acetaminophen use during pregnancy and childhood behavioural problems: Discrepancies between mother- and teacher-reported outcomes. Paediatr Perinat Epidemiol. 2020;34(3):299-308. doi:10.1111/ppe.12601.

[86] Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr. 2014 Apr;168(4):313-20. doi: 10.1001/jamapediatrics.2013.4914. PMID: 24566677.

Inoue K, Ritz B, Ernst A, et al. Behavioral Problems at Age 11 Years After Prenatal and Postnatal Exposure to Acetaminophen: Parent-Reported and Self-Reported Outcomes. *Am J Epidemiol*. 2021;190(6):1009-1020. doi:10.1093/aje/kwaa257.

Thompson JMD, Waldie KE, Wall CR, Murphy R, Mitchell EA, the ABC study group. Associations between Acetaminophen Use during Pregnancy and ADHD Symptoms Measured at Ages 7 and 11 Years. Hashimoto K, ed. PLoS ONE. 2014;9(9):e108210. doi:10.1371/journal.pone.0108210.

(4) Weschler Intelligence Scales for Children (WISC)[87]
(5) Weschler Primary and Preschool Scales of Intelligence (WPPSI)[88]
(6) Test for Everyday Attention at Five (TEACH-5)[89]
(7) Behavior Rating Scale of Executive Function (BRIEF)[90]
(8) Wide Range Achievement Test (WRAT)[91]
(9) Childhood Autism Spectrum Test (CAST)[92]
(10) Battelle Developmental Inventory (BDI)[93]
(11) Peabody Picture Test (PPT)[94]

Stergiakouli E, Thapar A, Davey Smith G. Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding. JAMA Pediatr. 2016;170(10):964. doi:10.1001/jamapediatrics.2016.177.

Golding J, Gregory S, Clark R, Ellis G, Iles-Caven Y, Northstone K. Associations between paracetamol (acetaminophen) intake between 18 and 32 weeks gestation and neurocognitive outcomes in the child: A longitudinal cohort study. Paediatr Perinat Epidemiol. 2020;34(3):257-266. doi:10.1111/ppe.12582.

Tovo-Rodrigues L, Schneider BC, Martins-Silva T, et al. Is intrauterine exposure to acetaminophen associated with emotional and hyperactivity problems during childhood? Findings from the 2004 Pelotas birth cohort. BMC Psychiatry. 2018;18(1):368. doi:10.1186/s12888-018-1942-1.

Rifas-Shiman SL, Cardenas A, Hivert M, Tiemeier H, Bertoldi AD, Oken E. Associations of prenatal or infant exposure to acetaminophen or ibuprofen with mid-childhood executive function and behaviour. Paediatr Perinat Epidemiol. 2020;34(3):287-298. doi:10.1111/ppe.12596.

[87] Laue HE, Cassoulet R, Abdelouahab N, et al. Association Between Meconium Acetaminophen and Childhood Neurocognitive Development in GESTE, a Canadian Cohort Study. Toxicol Sci. 2019;167(1):138-144. doi:10.1093/toxsci/kfy222.

[88] Liew Z, Ritz B, Virk J, Arah OA, Olsen J. Prenatal Use of Acetaminophen and Child IQ: A Danish Cohort Study. Epidemiology. 2016;27(6):912-918. doi:10.1097/EDE.000000000000054.

[89] Liew Z, Bach CC, Asarnow RF, Ritz B, Olsen J. Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years. Int J Epidemiol. 2016;45(6):dyw296. doi:10.1093/ije/dyw296.

[90] Liew Z, Bach CC, Asarnow RF, Ritz B, Olsen J. Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years. Int J Epidemiol. 2016;45(6):dyw296. doi:10.1093/ije/dyw296.

Rifas-Shiman SL, Cardenas A, Hivert M, Tiemeier H, Bertoldi AD, Oken E. Associations of prenatal or infant exposure to acetaminophen or ibuprofen with mid-childhood executive function and behaviour. Paediatr Perinat Epidemiol. 2020;34(3):287-298. doi:10.1111/ppe.12596.

[91] Bertoldi AD, Rifas-Shiman SL, Boing AC, et al. Associations of acetaminophen use during pregnancy and the first year of life with neurodevelopment in early childhood. Paediatr Perinat Epidemiol. 2020;34(3):267-277. doi:10.1111/ppe.12632.

[92] Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int J Epidemiol. 2016;45(6):dyw115. doi:10.1093/ije/dyw115

[93] Tovo-Rodrigues L, Carpena MX, Martins-Silva T, Santos IS, Anselmi L, Barros AJD, Barros FC, Bertoldi AD, Matijasevich A. Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development. Paediatr Perinat Epidemiol. 2020 May;34(3):278-286. doi: 10.1111/ppe.12649. Epub 2020 Mar 20. PMID: 32196712.

[94] Bertoldi AD, Rifas-Shiman SL, Boing AC, et al. Associations of acetaminophen use during pregnancy and the first year of life with neurodevelopment in early childhood. Paediatr Perinat Epidemiol. 2020;34(3):267-277. doi:10.1111/ppe.12632.

(12) Conners Kiddie Continuous Performance Test (K-CPT)[95]
(13) Development Well-Being Assessment Questionnaire (DAWBA)[96]
(14) Behavioral Assessment System Children[97]
(15) Emotionality, Activity and Shyness Questionnaire (EAS)[98]

In addition to screening tools of this type, some studies have used even less formal metrics such as parental rating of language and grammar abilities,[99] or the number of words a child knows by a certain age.[100] The results of these studies are highly inconsistent, frequently reaching contrary results using the same or similar measurements. Although I do not believe these studies inform the causation analysis, I have provided a detail summary of them in Appendix 2.

One study involving a screening tool, ***Avella-Garcia et al. 2016***,[101] merits special discussion here, because both Dr. Baccarelli and Dr. Cabrera incorrectly refer to it as a study evaluating ASD. Avella-Garcia and colleagues evaluated six different tools, none of which equates to an ASD diagnosis. The one most related to ASD is the Childhood Autism Screening

---

[95] Thompson JMD, Waldie KE, Wall CR, Murphy R, Mitchell EA, the ABC study group. Associations between Acetaminophen Use during Pregnancy and ADHD Symptoms Measured at Ages 7 and 11 Years. Hashimoto K, ed. PLoS ONE. 2014;9(9):e108210. doi:10.1371/journal.pone.0108210.

[96] Ruisch IH, Buitelaar JK, Glennon JC, Hoekstra PJ, Dietrich A. Pregnancy risk factors in relation to oppositional-defiant and conduct disorder symptoms in the Avon Longitudinal Study of Parents and Children. J Psychiatr Res. 2018;101:63-71. doi:10.1016/j.jpsychires.2018.02.020.

Golding J, Gregory S, Clark R, Ellis G, Iles-Caven Y, Northstone K. Associations between paracetamol (acetaminophen) intake between 18 and 32 weeks gestation and neurocognitive outcomes in the child: A longitudinal cohort study. Paediatr Perinat Epidemiol. 2020;34(3):257-266. doi:10.1111/ppe.12582.

[97] Baker BH, Lugo-Candelas C, Wu H, et al. Association of Prenatal Acetaminophen Exposure Measured in Meconium With Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity. JAMA Pediatr. 2020;174(11):1073-1081. doi:10.1001/jamapediatrics.2020.3080.

[98] Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Annotations and Reflections: Response to "Pregnancy and Paracetamol: Methodological Considerations on the Study of Associations between In Utero Exposure to Drugs and Childhood Ne. Basic Clin Pharmacol Toxicol. 2015;116(1):6-8. doi:10.1111/bcpt.12339.

Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MMHJ, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero : a propensity score matched cohort study. Int J Epidemiol. 2016;45(6):dyw192. doi:10.1093/ije/dyw192.

Golding J, Gregory S, Clark R, Ellis G, Iles-Caven Y, Northstone K. Associations between paracetamol (acetaminophen) intake between 18 and 32 weeks gestation and neurocognitive outcomes in the child: A longitudinal cohort study. Paediatr Perinat Epidemiol. 2020;34(3):257-266. doi:10.1111/ppe.12582.

[99] Skovlund E, Handal M, Selmer R, Brandlistuen RE, Skurtveit S. Language competence and communication skills in 3-year-old children after prenatal exposure to analgesic opioids. Pharmacoepidemiol Drug Saf. 2017;26(6):625-634. doi:10.1002/pds.4170.

[100] Bornehag CG, Reichenberg A, Hallerback MU, et al. Prenatal exposure to acetaminophen and children's language development at 30 months. Eur Psychiatry. 2018;51:98-103. doi:10.1016/j.eurpsy.2017.10.007.

[101] Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int J Epidemiol. 2016;45(6):dyw115. doi:10.1093/ije/dyw115.

Test (CAST), but while CAST tests for certain autism symptoms, it is not a test for ASD.[102] Dr. Baccarelli states that CAST has 100% sensitivity and 97% specificity for ASD with a cut-off of 15 or more points. But the same paper that reports these data also reports that CAST has a positive predictive value of only 50%.[103] In other words, essentially all children with autism will score 15 or more, and the vast majority of children without autism will score below 15. But because ASD is a relatively rare condition, just half of children who score 15 or above *actually* meet the criteria for ASD. Additionally, the analysis in Avella-Garcia et al. 2016 is not limited to scores above 15 points, making the sensitivity and specificity rates provided by Dr. Baccarelli irrelevant to the study's analysis.

In any event, to the extent that Avella-Garcia speaks to the questions at issue in this litigation at all, it tends to show that acetaminophen use does not affect CAST scores. CAST scores for all children were not significantly associated with in utero acetaminophen exposure: aβ=0.08; CI: -0.28-0.44. Efforts to construct a dose-response showed that neither "sporadic" nor "persistent" use of acetaminophen was associated with a significant change in CAST scores.[104] When the study group was broken down by sex, however, boys showed significantly higher CAST scores, while girls showed significantly lower CAST scores. These results are inconsistent with at least one prior study that has shown that acetaminophen has the opposite sex effects.[105]

Another non-diagnostic study included by Dr. Baccarelli when assessing ASD is ***Leppert et al. 2019.***[106] Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), the same cohort as Avella-Garcia, Leppert and colleagues set out to study genetic confounding by examining whether "maternal polygenic risk scores [(PRS)] for neurodevelopmental disorders" are associated with prenatal and early-life exposures of their children. (A polygenic risk score is a risk score assigned to an individual that measures that individual's risk of disease based on their

---

[102] Gharamaleki F, Bahrami B, Masumi J. Autism screening tests: a narrative review. J Public Health Res. 2022 Jan 31; 11(1): 2308.

[103] Williams J, Scott F, Stott C, Allison C, Bolton P, Baron-Cohen S, Brayne C. The CAST (Childhood Asperger Syndrome Test): test accuracy. Autism. 2005 Feb;9(1):45-68. doi: 10.1177/1362361305049029. PMID: 15618262.

[104] Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int J Epidemiol. 2016;45(6):dyw115. doi:10.1093/ije/dyw115.

[105] Liew Z, Ritz B, Virk J, Arah OA, Olsen J. Prenatal Use of Acetaminophen and Child IQ: A Danish Cohort Study. Epidemiology. 2016. November;27(6):912–8. 10.1097/EDE.0000000000000540.

[106] Leppert B, Havdahl A, Riglin L, et al. Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures. JAMA Psychiatry. 2019;76(8):834. doi:10.1001/jamapsychiatry.2019.0774.

genes.) As part of this process, the authors obtained data on in utero acetaminophen exposure and ASD symptoms, and calculated an association. The authors found no association between maternal acetaminophen exposure and an ASD symptoms: RR=0.76, 95% CI: 0.51-1.13.

Dr. Baccarelli discounts the results from Leppert et al. 2019, stating that because the acetaminophen had only a "supportive role . . . in the paper," it "was only adjusted by child's age at the time of ASD assessment and sex," which Dr. Baccarelli contends was "not adequate to control confounding."[107] I agree with Dr. Baccarelli that the results would provide stronger evidence if the data had been adjusted for additional confounders. I disagree that this shortcoming provides a reason to ignore—or even discount—the results of the study showing no effect. As I noted above, in other studies addressing the relationship between acetaminophen and ASD, including the Liew and Ji studies,[108] the observed association has gotten weaker, not stronger, after adjusting for additional potential confounders. This makes sense because some of the most obvious confounders—such as confounding by indication for maternal fever—would bias results toward showing a positive association. Thus, the results of the Leppert study, when coupled with the results from Ji et al. 2018, further suggest that in utero acetaminophen exposure is not associated with increased ASD risk.

1. Meta-Analyses Addressing Neurobehavioral Outcomes

There are three meta-analyses that seek to address the literature involving acetaminophen exposure and ASD as well as the literature involving the proxy studies.[109] But the data are simply insufficient to meta-analyze. The most recent group to attempt a meta-analysis related to ASD ultimately found that doing so was impossible because "[t]here w[ere] an insufficient number of comparable studies due to heterogeneity in methodology."[110] Other commenters have made a similar critique.[111]

---

[107] Baccarelli Rep. at 1000.

[108] In Liew et al. 2016 the crude HR for ASD was 1.22, while the fully adjusted HR was 1.19 (1.04-1.35). In Ji et al. 2018 the most-adjusted model reported lower odds ratios than the unadjusted model for each acetaminophen metabolite. For total burden, for example, the effect of above median exposure went from 1.94 (0.92-4.08) to 1.39 (0.59-3.27).

[109] These meta-analyses also examined literature surrounding ADHD and its proxies, and those portions of the studies are discussed below.

[110] Ricci C, Albanese C, Pablo L In utero acetaminophen exposure and child neurodevelopmental outcomes: Systematic review and meta-analysis Paediatr Perinat Epidemiol. 2023;00:1–12.

[111] Damkier P. RE: "PRENATAL EXPOSURE TO ACETAMINOPHEN AND RISK FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER AND AUTISTIC SPECTRUM DISORDER: A SYSTEMATIC REVIEW,

As discussed above, only a handful of studies have used diagnosed ASD as the study endpoint, while the bulk of the studies use other tests and tools. And although there are established techniques to perform a meta-analysis with somewhat heterogeneous data sets, the various screening and language studies at issue here have too little in common to be combined, even using those tools, without rendering the results meaningless.

Moreover, meta-analyses are subject to the same limitations as the underlying studies on which they rely. Unmeasured or residual confounding, selection bias, and exposure misclassification, if present in the underlying studies, will also be present in the results from a meta-analysis.

Despite their very limited utility as a result of these limitations, I summarize the major meta-analyses below. While one of the three groups that sought to perform a meta-analysis found that the lack of data made it methodologically inappropriate to undertake such an approach, the other two groups pooled highly heterogeneous sets of data and found very small associations between acetaminophen exposure in utero and the various outcomes of interest.

Masarwa et al. 2018. Masarwa and colleagues[112] pooled five studies (Streissguth et al. 1987;[113] Brandlistuen et al. 2013;[114] Liew et al. 2016;[115] Avella-Garcia et al. 2016;[116] Stergiakouli et al. 2016[117]). Of those studies, only one—Liew et al. 2016, discussed above—measured diagnosed autism. Avella-Garcia, 2016, also discussed above, involved the CAST screening test. The remaining three studies have little relation to ASD diagnosis. Streissguth et al. reported on

---

META-ANALYSIS, AND META-REGRESSION ANALYSIS OF COHORT STUDIES". Am J Epidemiol. 2018 Dec 1;187(12):2717-2718. doi: 10.1093/aje/kwy202. PMID: 30192922.

[112] Masarwa R, Levine H, Gorelik E, Reif S, Perlman A, Matok I. Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies. Am J Epidemiol. 2018;187(8):1817-1827. doi:10.1093/aje/kwy086.

[113] Streissguth AP, Treder RP, Barr HM, et al. Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements. Teratology. 1987;35(2):211-219. doi:10.1002/tera.1420350207.

[114] Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol. 2013;42(6):1702-1713. doi:10.1093/ije/dyt183.

[115] Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study. Autism Res Off J Int Soc Autism Res. 2016;9(9):951-958. doi:10.1002/aur.1591.

[116] Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int J Epidemiol. 2016;45(6):dyw115. doi:10.1093/ije/dyw115.

[117] Stergiakouli E, Thapar A, Davey Smith G. Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding. JAMA Pediatr. 2016;170(10):964. doi:10.1001/jamapediatrics.2016.177.

the effects of acetaminophen on "child IQ and attention."[118] Brandlistuen et al. involved "psychomotor development," "behavior," and "temperament," and noted the need for "future studies" to address actual "neurodevelopmental . . . diagnosis."[119] Finally, Stergiakouli et al. investigated "behavioral problems."[120]

Based on this heterogeneous literature, Masarwa and his colleagues calculated a small, but statistically significant, pooled risk ratio of 1.19 (CI: 1.14-1.25).[121] The authors acknowledged that "[g]reat caution should be advised when considering whether the link . . . is causal, because the available studies were susceptible to confounding and bias."[122] As discussed in greater detail below, the same study also performed a meta-analysis of ADHD risk. Notably, two years later, the lead author further analyzed ADHD risk and found the association to be "likely the result of bias."

Alemany et al. 2021.[123] Alemany and colleagues summarized data from six European population-based birth cohorts, including a total of 73,881 mother–child pairs. Only one of these cohorts had any data on ASD diagnosis. Using the six cohorts, the authors primarily sought to evaluate "ASD symptoms," using screening tools—DAWA, CAST, and two subscales from the CBCL.[124] Children were assessed between 4 to 12 years of age. They set cut-off scores for each tool to classify "borderline or clinical" cases. Overall, 2.1% of children were classified as having "borderline/clinical" autism symptoms, with enormous variation among cohorts, likely reflecting

---

[118] Streissguth AP, Treder RP, Barr HM, et al. Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements. Teratology. 1987;35(2):211-219. doi:10.1002/tera.1420350207.

[119] Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol. 2013;42(6):1702-1713. doi:10.1093/ije/dyt183

[120] Stergiakouli E, Thapar A, Davey Smith G. Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding. JAMA Pediatr. 2016;170(10):964. doi:10.1001/jamapediatrics.2016.177.

[121] This calculation was later cited in Kim et al. 2019. Dr. Baccarelli purports to rely on this paper, but it added no additional analysis or data beyond that included in Masarwa's analysis.

[122] Masarwa R, Levine H, Gorelik E, Reif S, Perlman A, Matok I. Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies. Am J Epidemiol. 2018;187(8):1817-1827. doi:10.1093/aje/kwy086

[123] Alemany S. Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: Meta-analysis in six European population-based cohorts. Eur J Epidemiol. 2021;36:12. doi:https://doi.org/10.1007/s10654-021- 00754-4.

the heterogeneous tools used.[125] In one, 12.9% were classified as having autistic symptoms, a rate that necessarily means a substantial number of neurotypical children were misclassified.

From this series of metrics, Alemany and colleagues calculated a small association between acetaminophen exposure and autism symptoms: OR 1.19; CI 1.07-1.33.[126] As with the original Masarwa study, this small association is likely the result of bias and/or confounding. The data were adjusted for "mental health during pregnancy," but not for any other type of parental or familial metal health history or genetic factors.[127]

Finally, ***Ricci et al. 2023***[128] set out to perform a meta-analysis, but found the data too limited to do so. Instead, the authors offered a narrative summary that suggested a potential association between ASD and acetaminophen exposure, but noted that "the certainty of evidence on this topic is low" and that "more research also is needed."

In summary, meta-analyses assessing maternal acetaminophen use and neurobehavioral developments do not provide evidence relevant to analyzing whether a causal link exists between maternal acetaminophen use and ASD development in offspring.

C. The Bradford Hill Considerations Do Not Support A Causal Link

Because a "perfectly clear-cut" association between in utero acetaminophen exposure and occurrence of ASD in offspring is not present, an analysis of the Bradford Hill criteria is not called for in this instance. As Hill explained before outlining his nine considerations, before evaluating causation, studies must "reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to chance."[129] And as noted above, the literature is

---

[125] Alemany S. Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: Meta-analysis in six European population-based cohorts. Eur J Epidemiol. 2021;36:12. doi:https://doi.org/10.1007/s10654-021- 00754-4.

[126] In supplemental materials, the authors reported a similar, but slightly smaller, association with hospital diagnosis of ASD. Those data came from the Danish National Birth Cohort and (unsurprisingly) are similar to the data in Liew et al., supra, which used the same cohort.

[127] Alemany S. Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: Meta-analysis in six European population-based cohorts. Eur J Epidemiol. 2021;36:12. doi:https://doi.org/10.1007/s10654-021- 00754-4

[128] Ricci C, Albanese C, Pablo L In utero acetaminophen exposure and child neurodevelopmental outcomes: Systematic review and meta-analysis Paediatr Perinat Epidemiol. 2023;00:1–12.

[129] Hill A B (1965). The environment and disease: association or causation? Proceedings of the Royal Society of Medicine, 58(5), 295–300.

insufficient to demonstrate a "clear cut" association between maternal acetaminophen exposure during pregnancy and ASD in offspring.[130]

Nonetheless, even assuming the association between in utero acetaminophen exposure and ADHD reported in the literature were sufficiently clear to merit application of the Bradford Hill considerations, the literature would not support a causal inference, Below, I discuss why the Bradford Hill criteria are not satisfied.

1. The Strength Of Association Factor Is Not Met

The first Bradford Hill criterion, strength of association, considers how strong the association is that has been reported in the literature. The stronger the association between a risk factor and the outcome, the more likely the relationship is to be causal.

To the extent studies have reported *any* increase in the risk of ASD or ASD-related symptoms among children whose mothers took acetaminophen while pregnant, those studies found small associations in the neighborhood of 1.2, meaning that ASD occurs about 1.2 times as frequently (20% more often) in exposed groups than unexposed groups. Liew et al. 2016 reported a crude hazard ratio of 1.22 and an adjusted hazard ratio of 1.19. Both meta-analyses of ASD symptoms also settled on risk or odds ratios of 1.19.[131] Ji et al. 2020 reported much higher odds ratios, up to 3.62 for the most exposed cohort, but that study is an outlier. Even plaintiffs' expert Dr. Cabrera terms the associations at issue "moderate"[132] and, at another point, acknowledges that "an odds ratio between 1 and 2 is deemed low."[133]

Dr. Baccarelli argues at length that "[e]xposures that are common can cause high numbers of cases even with small relative risks."[134] But the fact that an association may have a significant impact on public health if it is causal is not relevant in determining *whether* an exposure is causal

---

[130] Hill A B (1965). The environment and disease: association or causation? Proceedings of the Royal Society of Medicine, 58(5), 295–300.

[131] Masarwa R, Levine H, Gorelik E, Reif S, Perlman A, Matok I. Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies. Am J Epidemiol. 2018;187(8):1817-1827. doi:10.1093/aje/kwy086 (1.19 risk ratio).

Alemany S. Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: Meta-analysis in six European population-based cohorts. Eur J Epidemiol. 2021;36:12. doi:https://doi.org/10.1007/s10654-021- 00754-4 (1.19 odds ratio).

[132] Cabrera Rep. at 135.

[133] Cabrera Rep. at 195.

[134] Baccarelli Rep. at 25.

or whether it is a result of factors such as bias and confounding. Dr. Baccarelli also notes that some weak associations have ultimately proven causal, such as the association between secondhand smoke and cancer. But that scenario, in which there was an obvious causal mechanism, clear support by analogy, and over 50 consistent epidemiological studies in over 20 countries, is an example of the type of evidence that is lacking here.[135]

The reason small associations are considered poor evidence of causation is that they are easily explained by bias, confounding, random chance, or other factors. In the seminal paper that first articulated the Bradford Hill framework, Dr. Hill explained that a weak association is far more likely to be caused by "some features of life that may go hand in hand with" the association, while "pronounced" association (such as the 20-30 times risk of lung cancer in heavy smokers) are much more difficult to explain absent causation.[136] That consideration is particularly relevant here given the many potential biases that complicate the relationship between acetaminophen and ASD.

One example is exposure and misclassification bias. Although the cohort design of many of the studies at issue may limit misclassification bias based on the sort of flawed recollection that arises in the case-control design, the problem is not eliminated. For example, Liew et al. 2016 relied on maternal interviews at 12- and 30-weeks gestation, but use of an over-the-counter medication like acetaminophen can be forgotten in a matter of days. Importantly, this bias may be differential (i.e., it may be more likely to arise among those with a genetic confounder for ASD). Because of the strong genetic basis of ASD, mothers of children with the disorder are far more likely to have the disorder and its attendant symptoms themselves. These include anxiety, preservation, and insistence on routine: all things that would make them more likely to remember and record their use of over-the-counter medications.[137] Relatedly, research on retention in longitudinal studies suggests that those with conditions like anxiety, which are themselves

[135]Office of the Surgeon General (US); Office on Smoking and Health (US). The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2004, 14. PMID: 20669512.

[136] Hill A B (1965). The environment and disease: association or causation? Proceedings of the Royal Society of Medicine, 58(5), 295–300.

[137] Bekkhus M, Lee Y, Nordhagen R, Magnus P, Samuelsen SO, Borge AIH. Re-examining the link between prenatal maternal anxiety and child emotional difficulties, using a sibling design. Int J Epidemiol. 2018 Feb 1;47(1):156-165. doi: 10.1093/ije/dyx186. PMID: 29024982; PMCID: PMC5837524.

associated with ASD and ASD risk, are less likely to drop out.[138] This differential bias could be considerable. For instance, in Liew et al. 2016, 60% of the women in the cohort failed to complete the three required interviews during pregnancy and after giving birth.[139]

Confounding generally is an important concern that has not been properly addressed in the literature assessing ASD diagnosis. Confounding is particularly concerning in the context of ASD because there is still much that is unknown about the causes of ASD. Therefore, even where studies attempt to adjust for known confounders (such as maternal age), they are unable to account for the unknown risk factors.

The first and most significant potential source of confounding is genetics. As I explained earlier in this report, it is beyond dispute that ASD is highly heritable. Dr. Liew explained in a commentary on the Avella-Garcia study that "[i]f the genes causing autism spectrum conditions also lead to frequent use of medication, including a common painkiller like acetaminophen, a non-causal backdoor path is open."[140] Despite this clear possibility, none of the studies of ASD has adequately addressed the possibility of genetic confounding. None of the studies that use ASD diagnosis as an endpoint has applied either a sibling control or a negative control to limit genetic confounding. Nor have any of them used other metrics such as genetic risk scores. Some do not even control for maternal mental health,[141] and those that do use insufficient metrics that may not capture ASD (much less ASD risk), such as "mother's psychiatric illness."[142] Although none of these strategies will fully account for the influence of genetic confounding on

---

[138] Dupuis M, Strippoli MP, Gholam-Rezaee M et al Mental disorders, attrition at follow-up, and questionnaire non-completion in epidemiologic research Int J Methods Psychiatr Res. 2019;28:e1805.

de Graaf R, Bijl RV, Smit F, Ravelli A, Vollebergh WA. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Am J Epidemiol. 2000 Dec 1;152(11):1039-47. doi: 10.1093/aje/152.11.1039. PMID: 11117613.

[139] Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study. Autism Res Off J Int Soc Autism Res. 2016;9(9):951-958. doi:10.1002/aur.1591.

[140] Olsen J, Liew Z. Commentary: Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int J Epidemiol. 2016 Dec 1;45(6):1996-1997. doi: 10.1093/ije/dyw169. PMID:27401730.

[141] E.g., Ji. Y, Azuine RE, Zhang Y, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. JAMA Psychiatry. 2020;77(2):180. doi:10.1001/jamapsychiatry.2019.3259.

[142] E.g., Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study. Autism Res Off J Int Soc Autism Res. 2016;9(9):951-958. doi:10.1002/aur.1591.

any reported measure of association, to ignore this issue altogether renders the results less compelling.

Studies of other purported risk factors for ASD demonstrate just how important genetic confounding is in this context. The associations of these other factors, which are often of similar magnitude, have repeatedly been attenuated with use of a sibling control for genetic risk, as shown in the table below.

Study	Risk Factor	Risk Without Sibling Control	Risk with Sibling Control
Oberg 2016	Labor induction	aHR = 1.19, 95% CI 1.13, 1.24	aHR = 0.99, 95% CI 0.88, 1.10
Yang 2017	SSRI	aHR = 1.43, 95% CI 1.18, 1.74	aHR = 0.74, 95% CI 0.34, 1.59
Kalkbrenner 2020	Smoking	aHR = 1.19, 95% CI 1.14, 1.25	aHR = 0.86, 95% CI 0.64, 1.15
Zhang 2021	C-section: intrapartum (IP) and planned (PL)	aHR_{IP} = 1.26, 95% CI 1.19, 1.33 aHR_{PL}= 1.30, 95% CI 1.22, 1.37	aHR_{IP} = 1.07, 95% CI 0.95, 1.20 aHR_{PL} = 0.91, 95% CI 0.79, 1.04
Curran 2015	C-section elective C-section emergency	aOR = 1.21, 95% CI 1.15, 1.27 aOR = 1.15, 95% CI 1.10, 1.20	aOR = 0.89, 95% CI 0.76, 1.04 aOR = 0.97, 95% CI 0.85, 1.11
Brynge 2022	Maternal infection	aHR = 1.16, 95% CI 1.09, 1.23	aHR = 0.94, 95% CI 0.82, 1.08
Hegvik 2023	Epidural analgesia (pooled)	aHR = 1.12, 95% CI 1.10, 1.14	aHR = 0.98, 95% CI 0.93, 1.03
Ren 2022	Epidural labor analgesia	HR = 1.11, 95% CI 1.04, 1.18	HR = 1.03, 95% CI 0.84, 1.27

Some studies using non-diagnostic metrics have attempted to control for genetic confounding, but most of them relate to ADHD, not ASD. One study, Brandlistuen et al. 2013[143], found that the association between long-term acetaminophen use and behavioral problems as measured by the CBCL, as well as communication problems measured by the Ages and Stages Questionnaire, were not attenuated by sibling controls. But the authors did not suggest these

[143] Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol. 2013;42(6):1702-1713. doi:10.1093/ije/dyt183.

measures could be used as a proxy for ASD; to the contrary, they acknowledged that they "could not determine the clinical importance of the difference[s] observed."

A second source of confounding is confounding by indication, which, as discussed throughout my report, must be accounted for when addressing the impact of prenatal acetaminophen use on childhood ASD, because acetaminophen use may be a marker for the underlying condition for which it is taken. Studies have taken different approaches to confounding by indication, some of which have been inadequate. Liew et al. 2016 adjusted for the presence of diseases or conditions that may trigger use of acetaminophen: muscle and joint diseases, fever, inflammation, or infections. While this is a start, it ignores other potential indications such as pain and migraine and does not establish that acetaminophen was used for any of these diseases or conditions. Ji et al. 2018 and Ji et al. 2020 controlled only for maternal fever reported in medical records. That ignores all non-fever indications for acetaminophen. It also ignores the many incidences of fever that are self-treated and therefore not reported in records. The fact that a large portion of fevers are not adequately accounted for raises the possibility of confounding, since maternal fever itself has been shown to increase the risk of ASD in offspring.

Finally, the possibility of random chance cannot be discounted as an explanation for the weak associations observed. While statistical techniques such as p-values, confidence intervals, and significance findings are intended to reduce the possibility of chance findings, these techniques are less effective when many variables or outcomes are tested, which multiplies the opportunities for false positives, essentially overpowering the ordinary statistical tools. Here, Liew et al. 2016 reported results for 34 different comparisons and Ji. et al. 2020 reported associations for 24 different comparisons. Despite this, a Bonferroni adjustment (which helps control for multiple comparisons) was not performed.

For all of these reasons, the associations at issue are weak, to the extent they even exist, and are likely driven by bias, chance, and/or confounding. Thus, the first Bradford Hill factor is not satisfied with respect to the posited association between maternal acetaminophen use and the development of ASD in utero.

2. The Epidemiologic Data Are Inconsistent

Consistency of the association, the second Bradford Hill consideration, asks whether the same association exists in different studies, particularly those using different designs and different populations. Consistency is clearly not satisfied here. Among the studies that evaluated ASD

diagnosis as an endpoint, some found no associations,[144] one study found a statistically significant weak association,[145] and one found a moderate association.[146] It is hard to imagine any greater level of inconsistency. The two Ji et al. studies (2018 and 2020) are particularly striking. Using the same birth cohort, and similar metrics of blood metabolites as a metric for exposure at or near childbirth, the same lead author reached different results, with the 2018 study finding that "the risks of ASD diagnosis . . . were not significantly associated with" acetaminophen,[147] and the 2020 one finding that there was "a significant positive association."[148]

Some of the studies are also internally inconsistent. For instance, the results of Liew et al. 2016 suggest that maternal acetaminophen use is associated with ASD, but only with hyperkinetic disorder, although there is no etiological basis for such a distinction. By contrast, Ji et al. 2020 reported no significant association between acetaminophen and ASD comorbid with ADHD (a condition that would include ASD with hyperkinetic disorder, exactly what Liew et al. 2016 found to be elevated). Yet, it found that acetaminophen was significantly associated with both ADHD and ASD independently.[149]

The studies involving screening tools and language models are equally inconsistent. The studies using the CBCL are a good example. The CBCL contains various subscales. Some studies have shown no association between acetaminophen use and any subscale score.[150] And, among

---

[144] E.g., Leppert B, Havdahl A, Riglin L, et al. Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures. JAMA Psychiatry. 2019;76(8):834. doi:10.1001/jamapsychiatry.2019.0774.

Ji Y, Riley AW, Lee LC, et al. Maternal Biomarkers of Acetaminophen Use and Offspring Attention Deficit Hyperactivity Disorder. Brain Sci. 2018;8(127):15. doi:doi:10.3390/brainsci8070127.

[145] Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study. Autism Res Off J Int Soc Autism Res. 2016;9(9):951-958. doi:10.1002/aur.1591.

[146] Ji Y, Azuine RE, Zhang Y, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. JAMA Psychiatry. 2020;77(2):180. doi:10.1001/jamapsychiatry.2019.3259.

[147] Ji Y, Riley AW, Lee LC, et al. Maternal Biomarkers of Acetaminophen Use and Offspring Attention Deficit Hyperactivity Disorder. Brain Sci. 2018;8(127):15. doi:doi:10.3390/brainsci8070127.

[148] Ji Y, Azuine RE, Zhang Y, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. JAMA Psychiatry. 2020;77(2):180. doi:10.1001/jamapsychiatry.2019.3259.

[149] The lack of statistical significance for ASD comorbid with ADHD was not simply a product of small sample size. Ji et al. 2020 also reported a lower point estimate than for either ASD or ADHD alone.

[150] Tovo-Rodrigues, Carpena, Martins-Silva, Santos, Anselmi, Barros AJ, Barros FC, Bertoldi, Matijasevich. Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development. Paediatric and Perinatal Epidemiology. 2020;34(3):278-86.

those that have, the results remain inconsistent. Consider the portion of the test that focuses on behavioral problems. One study showed no association across the board,[151] another showed an association across the board,[152] and a third showed an association with "internalizing" behavior problems, but not "externalizing" ones.[153]

Dr. Baccarelli's response to these inconsistencies is to argue that "a set of results is consistent even if some of the results are not statistically significant."[154] But even if that were theoretically correct, the results are not even directionally consistent. For instance, the point estimate in Leppert et al. 2019 suggests a protective effect for acetaminophen exposure. In other cases, while the point estimates were positive, the confidence intervals were so wide that the results were not statistically significant or were too broad to be meaningful. As discussed above, despite the recent debate on the strengths and weaknesses of assessing statistical significance, tests for statistical significance are still a fundamental tool used by epidemiologists and other scientist to evaluate evidence.[155] In any event, Dr. Baccarelli does not cite any literature defining consistency in his unique way.

Because of the inconsistencies observed in the ASD studies, this Bradford Hill factor is not satisfied.

3. Specificity Is Not Satisfied

The third Bradford Hill consideration is specificity of the association between the exposure and the outcome. Causality is enhanced if an exposure is associated with a specific disease and not with a variety of diseases. Where there are a wide variety of outcome measures, this factor is more challenging to satisfy.

---

[151] Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MMHJ, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero : a propensity score matched cohort study. Int J Epidemiol. 2016;45(6):dyw192. doi:10.1093/ije/dyw192.

[152] Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol. 2013;42(6):1702-1713. doi:10.1093/ije/dyt183.

[153] Trønnes JN, Wood M, Lupattelli A, Ystrom E, Nordeng H. Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children. Paediatr Perinat Epidemiol. 2020 May;34(3):247-256. doi: 10.1111/ppe.12568. Epub 2019 Aug 25. PMID: 31448449; PMCID: PMC8285062.

[154] Baccarelli Rep. at 27 ("a set of results is consistent even if some of the results are not statistically significant").

[155] Harrington D, D'Agostino RB Sr, Gatsonis C, Hogan JW, Hunter DJ, Normand ST, Drazen JM, Hamel MB. New Guidelines for Statistical Reporting in the Journal. N Engl J Med. 2019 Jul 18;381(3):285-286. doi: 10.1056/NEJMe1906559. PMID: 31314974.

Dr. Baccarelli and Dr. Cabrera both concede that this consideration is not satisfied, and I agree. In fact, the arguments made by plaintiffs' experts underscore the point. For instance, Dr. Hollander discusses the "transdiagnostic model," which seeks to use the results from a litany of screening tools used to assess various behavioral, temperamental, intelligence, and neurological findings to support a casual inference. Not only does this disregard the diagnostic criteria for ASD in the DSM-V, but it is based on the belief that acetaminophen causes a host of neurodevelopmental issues—in other words, that any associations are non-specific. And Dr. Cabrera's focus on various physical ailments and conditions allegedly associated with acetaminophen exposure further emphasizes the lack of specificity.

4. Dose Response Cannot Be Established From The Epidemiological Data

Dose-response between the exposure and the risk of the outcome is the next consideration in the Bradford Hill causation analysis. If the risk of the outcome increases with increasing levels of exposure, the likelihood of a causal link is enhanced. To establish dose-response, the collection of accurate data on the timing and quantity of exposure is required. Dose response is particularly easy to study in the context of randomized trials or prescription medications where the number of doses taken is carefully monitored, but more difficult in the context of over the-counter-medications where many do not keep careful track of the number of doses taken.

Although some studies have sought to test a dose response, the available data do not support this Bradford Hill factor. In Liew et al. 2016, for example, "80% of the interviewed women were unable to recall" their specific dose, leading the researchers to ask respondents "to report use on a week-by-week basis allowing [them] to calculate trimester-specific" and duration of use.[156] The relationship between the number of weeks of use and the total dosage exposure is indirect at best. Some women may take low doses on a regular basis, while others might take larger doses more infrequently. One recent article that did seek to track specific dose information found that the link between trimesters of use and actual exposure was so tenuous that "characterizing exposure by number of trimesters is potentially misleading," and "relying upon the number of trimesters of use to proxy duration of use . . . would likely bias the categories of exposure, with some results

[156] Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study. Autism Res Off J Int Soc Autism Res. 2016;9(9):951-958. doi:10.1002/aur.1591.

possibly moving away from null."[157] Again, the imprecisions in these data might be differential rather than random. As discussed above, there is evidence to suggest that women who are at a higher risk of ASD are more likely to precisely and correctly report their exposure to medication. The Ji et al. studies from 2018 and 2020 attempted to construct dose responses based on exposure tertiles. But as discussed above, those studies only measure exposure at one point in time at or near childbirth. Moreover, to the extent the studies can measure dose response, the reported associations at each assessed interval do not show them gradually increasing as the alleged dose goes up. For example, in Liew et al. 2016, at 2-5 weeks use, the reported association is 1.23 (95% CI 1.02, 1.49), while the reported association declines to 1.16 (95% CI 0.91, 1.48) for 6-20 weeks of use.

Finally, any reported dose-response relationship could also be driven by confounding. In a study using data from the United States' MotherToBaby Cohort, 2,441 women kept daily acetaminophen diaries, recording complete dose and duration information for all exposures. 1,515 of the 2,441 (62%) women in the study reported acetaminophen use. Of these 1,515 women, 58% reported less than 10 days of use, 13% reported 10-19 days of use, 9% reported 20-44 days of use, and 9% reported 45 or more days of use. The authors found an association between increased use and potential confounding factors such as tobacco use, obesity, self-reported depression or anxiety, and antidepressant use. According to the study, "[c]ompared with women who did not use acetaminophen, women who used acetaminophen for more than 44 days had almost three times the prevalence of self-reported depression, four times the prevalence of anxiety, and three times the prevalence of other mental health disorders. Antidepressant use followed the same pattern.

[157] Bandoli, G., Palmsten, K., & Chambers, C. (2020). Acetaminophen use in pregnancy: Examining prevalence, timing, and indication of use in a prospective birth cohort. Paediatric and Perinatal Epidemiology, 34(3), 237–246. https://doi.org/10.1111/ppe.12595.

Women who used acetaminophen for the longest duration had five times the prevalence of antidepressant use compared with women who did not use acetaminophen."[158]

Thus, while some data raise the possibility of a dose-response relationship, there is not sufficient information to find that this consideration is satisfied.

5. Temporality (Time-Order) Is Uncertain

Time-order requires that the cause precede the effect in time. Of course, all in utero exposures predate the diagnosis of any disorder that is discovered after birth. But time order is difficult to determine in disorders with long latent periods or disorders with variable or uncertain time of onset or diagnosis. ASD is one such disorder. Research has not established the most vulnerable period for fetal development. Thus, it is impossible to know whether exposures actually preceded the biological changes that lead to ASD. Moreover, tying exposure of acetaminophen to any specific trimester, much less any particular week of pregnancy, is challenging because of the reliance on maternal recall when gathering data and the potential inaccuracies and bias inherent with data collected based on recollection. And the relevant studies that used biological measurements cannot establish time order, since their post-birth samples could only account at most for exposure during the final hours of pregnancy and childbirth.[159] Thus, this factor is not fully satisfied either.

6. The Epidemiological Data Lack Coherence

Causation is more likely if an association is coherent with the facts generally known about a disease. Examples include the fact that rates of lung cancer increased after rates of smoking increased, or that rates of mesothelioma increased after industrial usage of asbestos increased. Dr. Baccarelli argues that this criterion is met because the prevalence of ASD has increased over time and is supposedly higher in countries where acetaminophen use is widespread. But the prevalence of ASD is more a product of the increase in awareness and diagnosis than it is an increase in the true incidence of the disorder.

---

[158] Bandoli G, Palmsten K, Chambers C. Acetaminophen use in pregnancy: Examining prevalence, timing, and indication of use in a prospective birth cohort. Paediatr Perinat Epidemiol. 2020;34(3):237-246. doi:10.1111/ppe.12595.

[159] Ji Y, Riley AW, Lee LC, et al. Maternal Biomarkers of Acetaminophen Use and Offspring Attention Deficit Hyperactivity Disorder. Brain Sci. 2018;8(127):15. doi:doi:10.3390/brainsci8070127.

Ji Y, Azuine RE, Zhang Y, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. JAMA Psychiatry. 2020;77(2):180. doi:10.1001/jamapsychiatry.2019.3259.

Many factors have been reported to contribute to the increase in ASD diagnosis. Since 1980, the diagnostic criteria for ASD has been revised and expanded several times. In 2000, the CDC launched the "Learn the Signs. Act Early" campaign to improve the early identification of children with ASD. The broadening of the diagnostic parameters and the increased effort to diagnose children early in life has led to an increase in the number of children that are included under the umbrella of ASD. Because we have changed the manner in which cases are identified, including expanding the pool of health care providers who are trained to make the diagnosis, the reported prevalence has risen.

The manner by which childhood autism is diagnosed has changed significantly from Rutter's definition in 1967 (Rutter 1967) to the criteria outlined by the Diagnostic and Statistics Manual (used to standardize the diagnosis of different disease entities) including the DSM-III criteria in 1980, DSM-III-revised in 1987, DSM-IV in 1994, and DSM-V in 2013. At each step of this evolution, the criteria to be included as a case of ASD have changed and broadened, and the minimum number of criteria needed for the diagnosis of ASD has expanded from four essential criteria in Rutter's original definition, to 8 of 12 possible criteria under the DSM-IV, to a combination of persistent deficits in each of three areas of social communication and interaction plus at least two of four types of restricted, repetitive behaviors in DSM-V. Such changes result in challenges to the tracking of the change in prevalence rates over time.

Changes in prevalence that are not due to an increase in the incidence, i.e., not due to the actual risk of acquiring the disorder increasing, can occur as the result of many factors, including:

1. Substantial migration of affected children into or out of a community in order to gain access to educational and health-related services;
2. Changes in age of onset or age of recognition (an earlier age at diagnosis results in an apparent increase in prevalence);
3. Increased ascertainment of children with ASD and/or ADHD. For example, improved awareness through programs such as the CDC's "Learn the Signs. Act Early" campaign may lead to increases in diagnosis of ASD, which would result in an increase in prevalence; and
4. Change in diagnostic criteria such that children with milder symptoms are included under the ASD umbrella (an increase in the number of children included results in an apparent increase of prevalence).

The large increase in autism prevalence is almost certainly a result of these factors, and not simply an increase in the true incidence of autism. This position is supported by the vast majority of scientists, physicians and epidemiologists, who have addressed this topic in the published peer reviewed literature, which recognizes that the best explanations for the rise in ASD prevalence in the United States are changes in the diagnostic criteria and improved ascertainment. For example, a review of 47 epidemiology studies looking at the prevalence of autism concludes that the recent increase in prevalence is very likely connected to changes in diagnostic criteria, diagnostic substitution, and increased availability of services. The increase in children diagnosed with ASD often occurred at the same time as shifts in the ideas, diagnostic approaches, and services for children with ASD.[160]

Dr. Baccarelli's report states that the country's average prenatal acetaminophen consumption was found to be correlated with ASD prevalence. This, Dr. Baccarelli states, is consistent with what one would expect if acetaminophen were causally linked to neurodevelopmental disorders. Dr. Baccarelli's analysis ignores the four reasons I set forth above explaining the increase in prevalence. Additionally, it ignores one well-established, global trend, increased parental age at conception, which is a known risk factor.

7. No Experimental Evidence Examining Fetal Acetaminophen Exposure And ASD Exists

As plaintiffs' experts agree, experimental studies cannot be performed because it is unethical to perform such studies on pregnant women. Dr. Baccarelli suggests that animal and in vitro studies can be used to satisfy this approach. However, these studies are more appropriately considered when assessing biological plausibility.

8. Analogy Is Not Satisfied Because No Evidence Exists Of An Analogous Exposure And Outcome

As previously stated, in certain circumstances, analogy to other exposures can be considered to strengthen the association between an exposure and an outcome. This Bradford Hill consideration is mostly relevant for infectious disease exposure.

[160] Fombonne E, Quirke S, Hagen A. Prevalence and interpretation of recent trends in rates of pervasive developmental disorders. Mcgill J Med. 2009 Nov 16;12(2):73. PMID: 21152334; PMCID: PMC2997266.

I agree with Dr. Baccarelli that very little weight should be placed on this factor. As he states in his report, "[p]lacing too much weight on this factor would promote spurious associations as causal—because sometimes analogous drugs do not have analogous effects—and would also ignore truly causal association when no analogy was available."[161] However, he points to valproic acid as analogous to acetaminophen in terms of its impact of neurodevelopment, stating that "[v]alproic acid, like acetaminophen, has been shown to increase oxidative stress and deplete glutathione levels . . . one of the mechanisms by which Depakote is believed to cause NDDs."[162] This is a theoretical analogy only, as it is not grounded in actual data. The mechanism of action for acetaminophen's impact on neurodevelopment is hypothesized, but not yet supported, in humans. Therefore, I conclude that analogy is not satisfied.

9. Biological Plausibility Is Not Satisfied Because The Biological Mechanisms Are Hypothetical

The biological plausibility consideration requires an established biological mechanism, not simply a hypothesis about how such a mechanism might work. I understand that other experts will be addressing this consideration, but it merits a brief discussion here as well. Plaintiffs' experts' efforts to identify a biological mechanism depends largely on animal studies, which are of questionable relevance to begin with given the profound differences between the rodent brain and the human brain, and the fact that ASD is a uniquely human condition that affects uniquely human behaviors (e.g., speech). Moreover, because the etiology of ASD remains unknown, it is impossible to establish that one of the proposed mechanisms, such as oxidative stress, activation of the endocannabinoid system, or neuronal damage from epigenetic effects, is a plausible cause of ASD. These are all hypotheses. Even Bauer et al. 2018, a paper that Dr. Baccarelli relies on to state that "this criterion has been satisfied,"[163] goes no further than contending that "[t]here are several hypotheses . . . by which acetaminophen may interfere with normal brain development leading to neurodevelopmental disorders in children."[164]

* * *

[161] Baccarelli Rep. at 169.

[162] Baccarelli Rep. at 167.

[163] Baccarelli Rep. at 164.

[164] Bauer AZ, Kriebel D, Herbert MR, Bornehag CG, Swan SH. Prenatal paracetamol exposure and child neurodevelopment: A review. Horm Behav. 2018;101:125-147. doi:10.1016/j.yhbeh.2018.01.003.

For all of these reasons, it is my opinion to a reasonable degree of scientific certainty that it is unscientific, and indeed irresponsible, to conclude from the body of available scientific literature that maternal exposure to acetaminophen while pregnant can cause ASD in a child.

VII. ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

In this section, I address ADHD and the posited risk of ADHD posed by prenatal acetaminophen exposure. As I explain below, there are a number of recognized and suspected risk factors for ADHD, particularly genetics, family history of psychiatric disorders and infection and/or fever. Although eight cohort studies and one case-control study have looked at the potential association between prenatal acetaminophen exposure and a diagnosis of ADHD, their results do not support a causal conclusion. This is so because the study results are inconsistent, most of the studies fail to control for known confounders, such as genetics and confounding by indication (i.e., fever or infection), and those that do show an attenuation of risk from acetaminophen use, which tends to disprove causation. In addition, many of the studies relied upon by plaintiffs' experts used imprecise proxies for outcomes and/or lack reliable dose information. An evaluation of these studies and their limitations precludes a causal inference, as does an analysis under the Bradford Hill framework.

A. Background And Risk Factors

ADHD is typically a childhood-onset condition with symptoms of inattention, impulsivity and hyperactivity. Decades of research have documented and replicated key features of the disorder. It presents in about 5% of children, with little geographic or cross-cultural variation in prevalence, and often co-occurs with other conditions, including mood, anxiety, conduct, learning and substance use disorders.[165] ADHD is thought to be caused by a combination of factors, including genetic, neuro-biologic, and both endogenous and exogenous factors. Twin studies show that ADHD is strongly associated with heredity, and scientists have identified a number of genes that are believed to be linked to the disorder.

1. Genetics

Genetics are the predominant factor in the etiology of ADHD, with studies reporting heritability estimates of approximately 75%. One study of 894 individuals with ADHD and 1,135

[165] Belanger S, Andrews D, Gray C, Korkczak C. (2018) ADHD in children and youth: etiology, diagnosis and comorbidity. Pediatrics and Child Health 447-453.

of their siblings aged 5-17 years old found a nine-fold increased risk of ADHD in siblings of individuals with ADHD compared with siblings of controls.[166] It is also noted in the literature that twin studies in many different countries show high heritability rates for ADHD of around 71-90%.[167] In addition, adoption studies suggest that the familial factors of ADHD are attributable to genetic factors rather than shared environmental factors.[168]

Genome-wide association studies (GWAS) have implicated several common genetic variants associated with ADHD.[169] Studies have also revealed that rare insertions or deletions in genes account for part of ADHD's heritability.[170] Importantly, genetic risk factors for ADHD are also associated with certain pregnancy-related factors, which could act as confounders associations between these non-genetic factors and the development of ADHD in offspring.[171]

2. Family History Of Psychiatric Disorders

There is strong support in the epidemiologic literature for an increased risk of ADHD in offspring of parents with psychiatric disorders. For example, Liang et al. 2021 reported an

---

[166] Chen W, Zhou K, Sham P, Franke B, Kuntsi J, Campbell D, et al. DSM-IV combined type ADHD shows familial association with sibling trait scores: a sampling strategy for QTL linkage. Am J Med Genet B Neuropsychiatr Genet. 2008; 147B:1450–60.

[167] Thapar, Cooper, Eyre, & Langley. What have we learnt about the causes of ADHD? J Child Psychol Psychiatry. 2013 Jan;54(1):3-16. doi: 10.1111/j.1469-7610.2012.02611.x. Epub 2012 Sep 11. PMID: 22963644; PMCID: PMC357258.

Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005 Jun 1;57(11):1313-23. doi: 10.1016/j.biopsych.2004.11.024. Epub 2005 Jan 21. PMID: 15950004.

Nikolas MA, Burt SA. Genetic and environmental influences on ADHD symptom dimensions of inattention and hyperactivity: a meta-analysis. J Abnorm Psychol. 2010 Feb;119(1):1-17. doi: 10.1037/a0018010. PMID: 20141238.

Thapar, A., Holmes, J., Poulton, K., & Harrington, R. (1999). Genetic basis of attention deficit and hyperactivity. *The British Journal of Psychiatry, 174*(2), 105-111. doi:10.1192/bjp.174.2.105.

[168] Sprich S, Biederman J, Crawford MH, Mundy E, Faraone SV. Adoptive and biological families of children and adolescents with ADHD. J Am Acad Child Adolesc Psychiatry. 2000 Nov;39(11):1432-7. doi: 10.1097/00004583-200011000-00018. PMID: 11068899.

[169] Demontis D, et al. Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. Nat Genet. 2023 Feb;55(2):198-208. doi: 10.1038/s41588-022-01285-8. Epub 2023 Jan 26. Erratum in: Nat Genet. 2023 Mar 1;: PMID: 36702997.

[170] Faraone SV, Larsson E. Genetics of attention deficit hyperactivity disorder Molecular Psychiatry (2019)24:562–575https://doi.org/10.1038/s41380-018-0070-0.

Belanger S, Andrews D, Gray C, Korkczak C. (2018) ADHD in children and youth: etiology, diagnosis and comorbidity. Pediatrics and Child Health 447-453.

[171] Leppert B, Havdahl A, Riglin L, et al. Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures. JAMA Psychiatry. 2019;76(8):834. doi:10.1001/jamapsychiatry.2019.0774.